

# Cleveland Clinic Quarterly

*A Bulletin Published by*  
The Staff of the Cleveland Clinic  
CLEVELAND, OHIO

Vol. 2

APRIL, 1935

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No. 2

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## ETIOLOGY AND TREATMENT OF GALLBLADDER DISEASE

GEORGE CRILE, M.D.

Since the discovery by Pasteur of the bacterial causes of many diseases and the rise of pathology from the days of Virchow, practically all disease entities have been regarded from these two stand-points, viz., pathology and infection. The question may be raised whether it is not a mistake to attack the problem of gallbladder diseases with only these two points of view in mind. Instead of believing that the thyroid gland can originate a hyperplasia within itself, it is now known that hyperplasia is imposed upon the thyroid gland by factors from without. It is known also that peptic ulcer arises from influences originating outside itself. We now know that these diseases lie within the domain of pathologic physiology rather than in the field of pathologic morphology or of infection. Pathologic morphology and infection may be due to a primary pathologic physiology, which lays the foundation for their development, and this discussion of diseases of the liver and gallbladder is presented with this thesis in mind.

Any theory which attempts to explain the genesis of gall stones and of gallbladder disease must explain their distribution in nature and the sex and age incidence of the disease. It must account for the fact that gall stones occur more frequently in certain races, that they occur more frequently in women than in men, and further, that they occur more frequently in women who have borne children.

What is the distribution of gall stones in nature? Broadly speaking, this disease is less common among wild animals in captivity than in domestic animals, and the carnivora are more subject to the formation of gall stones than are the herbivora. This was found to be true by Dr. Herbert Fox, Pathologist at the Philadelphia Zoological Gardens, who has reported finding gall stones in but fourteen out of 6000 autopsies performed on wild animals which were in captivity.

Among human beings there is a significant distribution of gall stones and of gall stone disease. It has been observed that the highest incidence of gall stones is found among the Hebrew and Latin races while they are relatively uncommon in the colored race and among the Hindus, the Chinese, the Japanese and the Koreans, as compared with the Europeans and the Americans. Differences in diet among these peoples must, of course, be taken into account, since Walsh has shown that gall stones are more likely to occur in patients who have had a diet low in vitamins, especially in the fat-soluble vitamins A and D. Gallbladder disease is not found so frequently in people of a lower order of civilization or in persons who, though they may

belong to a higher order of civilization, have a negative philosophy of life.

It would seem, therefore, that there are certain factors operative in highly-developed, high-strung, emotional, active persons and in childbearing women that can change the concentration of the bile salts secreted by the liver cells, this concentration being due to a change in the activity of the cells of the liver. Ivy and Walsh and others have shown by their experimental work in dogs and by experiments in vitro that the outstanding factors that govern the maintenance of the cholesterol and pigment in solution in the bile are the bile salts and the fatty acids. It is readily seen that when gall stones or infection interfere with the free flow of bile in and out of the gallbladder, there results an immediate interference with the concentration of the bile salts and fatty acids and further formation of gall stones is promoted by the diminished concentration of the solvent bile salts. Thus, an infection, by interfering with the concentration of the bile, would probably promote the formation of gall stones. But the question is raised whether the infection is not the *result* rather than the *cause* of gall stones.

That this is the case is attested by the fact that it has been estimated that there are now in the United States twelve million people who have gall stones and do not know of their presence. Moreover, relatively few patients have an infected gallbladder or an abscess in the gallbladder without stones. Infection does not play the primary rôle in causing the depression of the function of the liver cells but rather depression of the function of liver cells occurs as the result of a general infection, acute or chronic, emotional excitation, pregnancy and excessive eating. Each of these conditions has the power of changing the concentration of the bile salts and in consequence promotes the formation of gall stones. Therefore, it is not infection, but altered function of the organism, which furnishes favorable conditions for the formation of gall stones, and those men and women whose livers are more often subjected to that kind of change, which will alter the concentration of the bile and the amount of the fatty acids, are the men and women in whom there is a high incidence of gall stones.

The key to the explanation of the above picture was provided by certain histological and biophysical researches instituted twenty-five years ago which have provided the explanation of certain facts regarding the incidence and behavior of gall stones.

A histologic examination was made of every organ and tissue in animals that had been subjected to insomnia, fear, physical injury, shock, prolonged anesthesia and infection. In every case histologic changes were observed in three organs and in three organs only—

## GALLBLADDER DISEASE

the brain, the liver and the adrenal glands. In the liver the cells lost their differential stainability—they became swollen and misplaced, the cytoplasm was vacuolated, the nuclei were crenated and the cell membranes were irregular. The most marked changes occurred in the cells nearest the periphery of the lobules. Later, identical changes were found in the liver cells of patients who had died from infection, from hyperthyroidism, or in any case in which exhaustion was due to the protraction or intensity of the disease. Later biophysical researches disclosed that, under the same conditions, changes took place in the temperature and in the electric conductivity, electric capacity and electric potential of the liver.

Hyperkineticism presupposes primarily to hyperactivity of the adrenal-sympathetic system. Pregnancy, infection, emotion, foreign proteins—all hyperkinetic conditions—produce an immediate change in the cells of the liver. Change in the cells of the liver in turn presupposes a change in the bile content; change in the bile content, as shown by experimental research, leads to the formation of gall stones.

It has been established by laboratory experimentation that the liver performs its function in part through direct nerve stimulation over the sympathetic system and in part through hormone action; and that for the performance of at least part of its function it must have a simultaneous hormone and nerve stimulation. The nerve supply of the liver is derived from the sympathetic and parasympathetic system, the nerve fibres passing along the blood vessels and the common duct. In addition to the nerve supply to the liver as a whole, each separate liver cell has its own nerve supply, not only on its outer border, but a filament of nerve tissue penetrates each separate cell.

One would expect to find that an organ, every unit of whose structure is thus wired, would have a close relationship with the great functions of the body. This rich sympathetic supply of the liver is of special importance as it supplies a connection between the adrenal glands and the liver. Experimental researches have shown that when the adrenals were removed, the liver cells undergo disintegration; while after decapitation, if the adrenals remain intact, the liver cells do not break down. Moreover, the injection of adrenaline increases the stainability of the liver cells followed by loss of stainability. To the extent, therefore, that the sympathetic innervation of the liver is interfered with, to that extent is the adrenal influence removed from the liver, and the diminished influence of the adrenals will be registered in the liver cells.

There is nothing more definitely established than that the injection of adrenline, the expression of an emotion, the presence of a foreign



protein or of an infection, or a great exertion, or a physical injury produces an increased activity of the energy system of the organism, and the liver is linked indissolubly with that energy system. All the factors that cause an increased output of adrenaline in the experimental laboratory have the power of changing, of modifying, of interfering with the cells of the liver, and, in consequence, with their production of bile.

Physical injury and anesthesia also produce changes in the liver cells, and this fact has a direct bearing upon the operative treatment of gallbladder disease, for it follows that the management of the patient should be directed primarily to the restoration of the already impaired liver cells and the protection of those cells from further damage.

The question then arises as to what treatment should be instituted for these highly-developed, high-strung, emotional, active persons and childbearing women whose liver cells have undergone changes which result in alteration in the concentration of the bile salts and formation of gall stones.

The surgical procedure to be preferred is cholecystectomy, unless the condition of the patient is such as to render this operation inadvisable, in which case conservative measures must be resorted to as the only alternative.

*Anesthesia:* Experimental researches have shown that physical trauma and inhalation anesthesia affect the liver cells. Therefore it is obvious that for the protection of liver function, minimum trauma must be inflicted and that the anesthesia must not be carried beyond the minimum degree necessary to secure the required relaxation. This is obtained in most cases by local, regional and splanchnic anesthesia with nitrous oxid analgesia. In obese patients, spinal anesthesia is preferred but it should never be employed in the presence of an associated high blood pressure or of nephritis. As an added precaution against the effects of the lowered blood pressure due to spinal anesthesia, a blood transfusion may be given just before the anesthetic is administered.

Our researches have shown also that every exhaustion-producing stimulus—anesthesia, physical injury, emotion, etc., reduces the temperature of the liver. Therefore, both the liver and the brain must be protected to the utmost against further cooling by the exposure of the viscera. To avoid such a condition which formerly was termed "liver shock", the surgeon must be prepared to execute every maneuver with the constant objective of protecting the liver against operative trauma, against interference with its nerve supply and against cooling of the intra-abdominal organs. In cases in which

## GALLBLADDER DISEASE

the hepatic function is low, it is best to defer operation and to administer a high carbohydrate diet and glucose solution intravenously until the liver shows evidence of restoration of its normal function.

*Operative technic:* The following points are essential in the technic of cholecystectomy: (1) The gall bladder must not be opened. (2) The liver tissue must not be injured or laid bare. (3) The cystic duct and the cystic duct alone should receive the ligature. (4) The common duct must not even be crowded by the ligature. (5) Not even a fragment of the base of the gallbladder should be left. (6) The field should constantly be kept so clear that an accessory or abnormal duct can be seen. (7) In general, the duct and the artery should be tied separately, although if the common pedicle is small, there would seem to be no risk in tying them together. (8) To prevent adhesions, to minimize oozing, to control the transudation of capillary bile, the raw surface of the liver, if any, should be closed by means of a fine, round, curved needle, the stump being buried beneath the suture line. Closure of the cystic duct with broad bladed, curved forceps is a most important step in the removal of the gallbladder so that no stones may be pushed into the common duct.

*Drainage:* Many, perhaps most, clean cholecystectomy wounds theoretically can be closed without drainage, yet occasionally there will be an unusual case, in which bile leaks in some unexplained way and bile peritonitis threatens or may even cause the death of the patient. The probable explanation is that some small aberrant bile duct, through which a small hepatic area is drained directly into the gallbladder, is unknowingly divided, so that after the wound is closed it oozes unnoticed until bile peritonitis is established. This occasional occurrence supplies the argument in favor of drainage in every case. This argument is the more convincing because bile peritonitis is one of the most difficult complications to recognize. The patient may appear very well for several days, and then suddenly, probably because of the gradual increase in the quantity of bile which has escaped, may become desperately ill.

*Prevention of Postoperative Complications:* Gallbladder infection and gall stones cause pain and indigestion as the result of the disturbance of the delicately balanced autonomic nervous system. If, in the removal of the gallbladder, the sympathetic nerves, which are almost devoid of shielding coats, are disturbed or injured or laid bare, postoperative digestive disturbances will occur, adhesions will form, and there will be a long course of pain and indigestion resembling the symptoms before the operation. It is not surprising

that there should be postoperative symptoms that are so similar to the pain and indigestion which accompany cholecystitis, since both before and after operation, the symptoms are caused by disturbance of the sympathetic and parasympathetic nerves.

A proof of the validity of this point of view is the fact, that to the extent that the autonomic nervous system is protected against postoperative scar, to that extent will postoperative pain and indigestion be diminished. Since the technic has been conducted scrupulously to avoid disturbing the sympathetic system, and the practice of a splanchnic block by injection of novocain through the posterior peritoneum in the region of the sympathetic complex has been instituted, painful indigestion, gas, etc., have been prevented in the later clinical course.

#### SUMMARY AND CONCLUSIONS

The highest incidence of gall stones is found among hyperkinetic and emotional persons. There is a higher incidence among women than among men and this is higher in women who have borne children. This is accounted for by the fact that those persons who are affected by the disease are those who are highly-developed, high-strung, emotional, active persons or pregnant women whose energy system has been subjected to increased activity. These factors change or modify the concentration of the bile salts secreted by the liver cells. Therefore, pathologic physiology rather than pathologic morphology and infection is responsible for the formation of gall stones.

The treatment of preference is cholecystectomy except in those cases in which this operation is inadvisable. The preoperative, operative and postoperative phases of the treatment must blend together so that they do not counteract each other. The establishment of chemical and nervous equilibrium by preoperative measures is extremely important and physical and mental rest and the re-establishment of the electrolytic and glucose balance contribute to the desired end. During the operation the depression of the protoplasm by the anesthetic, by a fall in blood pressure, by shock, by lowering of temperature, must be reduced to the absolute minimum. Sharp dissection and care in handling the sensitive tissues are imperative. When these general measures are employed, the immediate as well as the later course of patients subjected to operations on the gall-bladder and ducts is relatively smooth.

## UROLOGY AS A SPECIALTY\*

WILLIAM E. LOWER, M.D.

A little over twenty years ago, Hugh Cabot, in his presidential address before the American Urological Association, used the topic, "Is Urology Entitled to be Regarded as a Specialty?" He defined very clearly the meaning of the word specialty: "A department of medicine becomes a specialty when our knowledge of the diseases of this department becomes so far developed that it requires the whole time of any individual to keep abreast of the accumulating knowledge and still have time to devote to study of the problems presented." During the span of our own medical life, the knowledge of diagnosis and treatment of diseases of the genito-urinary tract has emerged from a comparatively obscure field into the realm of an almost exact science, through the efforts of those devoting their entire time to this special field of endeavor.

But without the rapid growth and development of other sciences, especially of chemistry and physics, and without the ingenious inventions and improvement in mechanical technology which has made our modern world what it is, urology would have gone little beyond the narrow limits which characterized the functions of the wandering lithotomists and uroscopists of olden times.

Diseases of the genito-urinary tract are not new. We have simply found ways of recognizing and distinguishing them. The Hindus are said to have "cut for stone" as early as 600 B. C. Lithotomists were mentioned by Hammurabi, and Hippocrates in his famous code on medical ethics, mentioned that only a trained lithotomist should "cut for stone." In certain families, the art of this particular operation was handed down from father to son through many generations. We urologists of the twentieth century are not the first to practice genito-urinary surgery as a means of livelihood.

The ancients were also skilled in the passing of sounds and catheters, and their prowess in this particular field probably has not been equalled, certainly not excelled, since their time. Uroscopy, that is, diagnosis by examination of the urine, was a favorite practice in the middle ages. Its protagonists claimed to be able to detect in the urine the presence of almost any physical abnormality or derangement, especially pregnancy. Practitioners of this art were repudiated as charlatans by more exact workers, but their claims may be regarded as a quaint prophesy of the modern method of diagnosis of pregnancy by a biologic test of the urine.

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\* Abridged from lecture given at the opening of the James Buchanan Brady Foundation, New York City, February 15, 1933.

The work of the anatomists constituted the foundation stone for the whole science of modern medicine and surgery, and their findings paved the way for those who came later. After the men who studied the structure of organs came the physiologists and clinicians who began to investigate and to study the functions of organs—a step really more important than a study of their structure.

Renal functional tests were not unknown to the earlier physician. Those clever medics who fed their patients asparagus or chicory, and then watched for the time of the appearance by odor of these substances in the urine, were using the same principles which was later employed in the dye tests of kidney function, and which have had such a prominent and important place in recent urologic practices.

Skilled surgeons operated on the genito-urinary tract long before the era of modern surgery, asepsis and anesthesia, and long before the dawn of modern urology as we know it. We still marvel at their skill and speed. Their shortcomings were not due to a lack of surgical technic, but to insufficient means of diagnosis of diseases of the genito-urinary tract.

Modern urology may be said to have begun with Nitze, whose cystoscope revolutionized the approach to the study of diseases of the kidneys and bladder. But without Edison's invention of the incandescent lamp, and the subsequent contribution of the x-ray by Röntgen, urology would still be relegated to the limbo of darkness. The development of our specialty literally has been entirely dependent on the light which these great scientists shed on the situation. Visualization of the entire urinary tract by means of the cystoscope and roentgenogram has made accurate diagnosis possible, and this has resulted in the development of the science of genito-urinary surgery to a high degree of perfection.

Following Nitze's original cystoscope, many mechanical devices were introduced into the practice of urology, and the mechanical evolution of instruments and the development of renal functional tests have contributed to placing this specialty on a sound and solid basis.

Thus the makings of a specialty were thrust upon the medical profession by the anatomists, physiologists, physicists, chemists, inventors, mechanics and lens grinders, but the status of urology has been made secure by those practitioners of medicine, who have devoted their entire time and attention to a study of this special field and to using and perfecting the instruments and means which have been placed in their hands. To keep abreast of the natural growth and development in the field has necessitated a limitation of interest.



## UROLOGY AS A SPECIALTY

Specialization has met the requirements and demands of modern life and medicine. Patients have given their approval to specialized departments of medicine and surgery, because of the superior service that has been rendered. Advancement in urology could never have come about so rapidly if certain men of great ability had not devoted their entire time and attention to a study of its problems. The public has been quick to recognize the resultant benefits of specialization, and to demand this type of service. Diseases which formerly were undiagnosed and untreated now fall into the category of more or less routine practice. In our own specialty, as an example, special study has resulted in much better service to elderly men suffering from hypertrophy of the prostate, a condition which formerly took a much greater toll in life and suffering.

But on the other hand, we have sometimes been accused, I think justly, of drawing the fine wires of specialization almost to the breaking point. In our enthusiasm and zest for supreme ability in our chosen field, we sometimes seem to lose sight of the fact that the genito-urinary system is, after all, a part of the human body, and that its function cannot be entirely isolated from the functions of the other parts of this complex organism.

Not only should the relationship of the special organs to the body as a whole be carefully studied and evaluated, but the cause of the symptoms should be thoroughly investigated in each case. Symptoms referable to the gastro-intestinal tract often occur when lesions of the upper urinary tract are present, and this fact must constantly be borne in mind, for, not infrequently, the cause of the symptoms will be sought by mistake within the peritoneal cavity. This common error has caused about 30 per cent of patients with right-sided ureteral and kidney stones to be subjected to appendectomies which failed to relieve the symptoms. The diagnosis of acute pyelitis also is often confused with that of appendicitis. Intestinal obstruction and ileus requiring surgical treatment have occurred as the result of kidney or ureteral stones, and hematuria, secondary to gall stones, has been recorded.

In the presence of some renal lesions, pain may be referred to the knee and the source of the trouble may be entirely overlooked. The relation of venereal and non-specific infections of the prostate to severe arthritis and joint symptoms is continually evident in practice. The presence of chronic sciatica in men past forty-five years of age should always suggest the possibility of the presence of malignant disease of the prostate and demands direct examination of this organ. Many infections originating in the genito-urinary organs manifest a variety of symptoms in other parts of the body. Hence the importance in genito-urinary practice of accessibility to prac-

tioners in other departments of medicine for consultation is obvious. At all times, the urologist must keep in mind that he is treating patients, not merely diseases.

Hence a good urologist must be qualified by training and experience to take a broad general view, not only of his own specialty, but also of the entire problem presented by the patient suffering from genito-urinary disease. He must be familiar, not only with his own diagnostic methods, but with the interrelationship of his specialty with roentgenology, general surgery, internal medicine, and endocrinology.

Some recent investigations have shown us that certain genito-urinary diseases, especially those of the prostate and testes, must be considered in relation to the general endocrine system. It would appear that future developments and knowledge in our field are likely to be based to a large extent on the advancement of biochemistry and of endocrinology. We already have shown experimentally a relationship between the testes and the prostate and the endocrine system which seems likely to be of great clinical significance.

Even within the limitations of the special field, too much emphasis on one phase of the work may prejudice or inhibit one's ability in another direction. Some devote all their time to diagnostic work and as a result are not capable of appreciating or coping with the surgical problems which present themselves. Others who know little else but venerology consider themselves trained urologists.

Then there are those who really are not specialists at all, and are not qualified either by training or experience to call themselves urologists, yet they pose as experts, in order to reap financial benefit. A qualified specialist in genito-urinary diseases can become so only at the expense of much time, money and work, and these pseudo-specialists can but bring our specialty into disrepute.

The urologist, or the genito-urinary surgeon, as I prefer to think of him, should be skilled in all the diagnostic methods, and also should be able to treat the patient adequately. A fundamental foundation of good general training in diagnosis and surgery is absolutely essential to any specialist. Some do not build on this strong foundation and fail because of this fundamental lack. Occasionally we hear criticism, and often rightly so, of the performance of operations on the genito-urinary tract by a general surgeon, but it is no worse for a general surgeon to operate unnecessarily because of a mistaken diagnosis, than it is for a urologist to make a correct diagnosis and fail to perform a successful operation because of lack of training in the proper surgical technic. A wide experience in the diagnosis and treatment of venereal diseases and in the clever use

## UROLOGY AS A SPECIALTY

of the cystoscope does not mean that a person is qualified to undertake difficult operations on the genito-urinary tract.

Moreover, the specialist in genito-urinary surgery must have sufficient general surgical training to be able to cope with pathologic lesions in proximity to his field. A vesical tumor may be secondary to a growth in the intestine. In such a case, the operation can not be divided between an abdominal and a genito-urinary surgeon. Either should be equal to the task before him.

No specialty is going to advance to its fullest extent if its practitioners are content to practice only the routine measures connected with it. Although our profession has been advanced by the evolution and perfection of mechanical instruments and appliances, perhaps too much attention has been paid to this phase of the work, with the result that other more important factors have been overlooked. Is there not a tendency among urologists to make some slight modification in an instrument or table, and to attach a new name to this equipment, rather than to devote the time to more fundamental and important investigations? The multiple modifications of genito-urinary implements add to the high cost of medical care. The expense of all these special gadgets, which bring an additional tax upon us, must be added to the patient's expense. This is true not only in urology but in all the specialties. I appreciate fully the rapid changes that are constantly being made in electrical equipment and that older models are becoming obsolete, but unless the change greatly benefits the patient, there should not be too great haste to adopt the newer models and modifications.

Fortunately for the advancement of our calling, with all our knowledge and instruments and tests and explorations, we can not always make a correct diagnosis or determine accurately the cause of a given lesion. If this were possible we should soon lose interest and there would be little or no incentive for further study, investigation and hard work.

But there remain as many problems to be solved as have ever been conquered. Urology has reached its present staunch position through the intelligence and hard work of a great many diligent devotees. And if the specialty is to be advanced further, we who are practicing urology must keep everlastingly at work, not only in employing what we already know, but also in reaching out constantly toward new facts and discoveries which may benefit the patient suffering from genito-urinary disease. I feel that too much time is devoted to technic and to modification of special instruments, and not enough to investigation of causes. We are well qualified to care for patients with urinary lithiasis, but we still know too little about the production of stones and the methods of preventing their forma-

tion. We should study the causes of prostatic hypertrophy and be able to anticipate its occurrence. We should learn more about the causes of urinary infections and why, in certain cases, in spite of every precaution, there is such a severe systemic reaction following cystoscopic examination.

However, much as we may desire to perform operations, the real task of the surgeon, according to Lord Moynihan, is to know how to cure diseases without operation. Such a time may be in the offing; my vision is not strong enough to see it as yet, but I am an optimist and I predict a great future in preventive medicine, and if urology advances as rapidly in the next twenty years as it has in the past, it will still be in the very front rank of medical achievement in this direction.

But in spite of Lord Moynihan's ultimatum, and of the trend toward fewer operations, many surgical problems still confront the genito-urinary surgeon. I feel certain that the surgical treatment of malignancy of the bladder could be extended and improved; that, perhaps, cystectomy should be performed more frequently, as the technic of transplantation of the ureters evolves and is perfected. There will always be the congenital anomalies and abnormalities to challenge the intelligence and skill of the surgeon; the problems presented by epispadias, hypospadias and exstrophy of the bladder will always confront us.

If the lofty structure of urology is to endure, we must be alert and ready to embrace the new knowledge which is sure to come. Urology has become a specialty because of the vast amount of knowledge which has been made accessible to us by the scientists and inventors of a past generation and by the industry and application of our contemporaries, and if it is to live and grow, as I know it will, it must keep pace with modern trends and discoveries. If those of the coming generation will light their candles from the torches carried by those who have brought the specialty to its present status, there will be no break in the steady progress of urology as a special branch of medicine.

## STUDIES IN BLOOD IODINE BY THE USE OF A NEW CHEMICAL METHOD\*

D. ROY McCULLAGH

*With the Technical Assistance of Valerian Picha*

### I. HISTORY

Harrington<sup>1</sup> and McClendon<sup>2</sup> have reviewed the history of the thyroid gland and the relation of iodine to that gland in a very complete manner. The present review, therefore, will be limited to a few statements especially relevant to the necessity for better technical methods in this field of biochemistry.

Iodine was discovered by Courtois<sup>3</sup> in 1812 and publicly announced by Clement<sup>4</sup> in 1813. Immediately following this publication, medical men observed that many of the substances containing large amounts of iodine were those substances, such as kelp, which had been useful in the treatment of diseases of the thyroid gland. This marked the birth of the study of iodine in connection with goiter, and since that time, biochemical investigations concerning the thyroid gland have been centered largely around the element iodine. Coindet<sup>5</sup> in 1820 used iodine as such in the treatment of thyroid disorders and by most authorities is said to have been the first to make therapeutic use of the new drug. However, a quotation<sup>†</sup> from Prout<sup>6</sup> indicates that iodine was first used in England in 1816.

"It may not be amiss to observe here that the author of the present volume first employed the hydriodate of potash as a remedy for goiter, in the year 1816, after having previously ascertained by experiments upon himself, that it was not poisonous in small doses as had been represented. Some time before the period stated, this substance had been found in certain marine productions; and it struck the author that burnt sponge (a well-known remedy for goitre) might owe its properties to the presence of Iodine, as this was his motive for making the trial. He lost sight of the case in which

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\* Reprinted by permission of the Western Journal of Surgery, Obstetrics and Gynecology from the Transactions of the American Association for the Study of Goiter, p. 117-141, 1934.

† These remarks constitute a footnote in Dr. Prout's paper, which interestingly bears the following rather comprehensive title "Chemistry, Meteorology and the Function of Digestion considered with reference to Natural Theology", by William Prout, M.D., F.R.S., Fellow of the Royal College of Physicians, London, William Pickering, 1834.

"Treatise VIII, of the Bridgewater Treatises on the Power, Wisdom and Goodness of God as manifested in the Creation."



the remedy was employed, before any visible alteration was made in the state of disease; but not before some of the most striking effects of the remedy were observed. The above employment of the compounds of Iodine in medicine was at the time made no secret; and so early as 1819, the remedy was adopted in St. Thomas's Hospital, by Dr. Elliotson, at the author's suggestion."

Ever since these early investigations, almost continuous research on this subject has been in progress and it appears that the greatest obstacle in the way of these researches has been the lack of a reliable method for the estimation of small quantities of iodine. One of many striking examples of this is the work of Chatin.<sup>7</sup> As early as 1853 Chatin had what now appears to be excellent evidence to prove that endemic goiter was always associated with a deficiency of iodine in air, water and soil. In one instance he demonstrated that in Saillon, a village on the Rhone, there was no endemic goiter until after a change of water supply which resulted in a considerable decrease in available iodine. The French Academy of Science investigated the matter and refused to accept Chatin's findings because of frequent contradictions. The Academy of Medicine, however, tested his theory by administering iodine, but used such large doses that the frequent occurrence of iodism caused them to discontinue the experiment.

It was largely on account of the independability of his chemical methods that Chatin was unable to convince his contemporaries that endemic goiter was caused by iodine deficiency. It seems probable that Chatin<sup>7</sup> himself was in grave doubt concerning the correctness of his observations. Therefore, because of the technical difficulties involved in the estimation of iodine, it was not until 1918 that Kimball and Marine,<sup>8</sup> using methods not dependent upon the determination of iodine, showed that endemic goiter was probably due to iodine deficiency in the diet.

It was not until 1914 that anything approaching a reliable method for the determination of iodine was introduced.<sup>10</sup> Kendall devised a modification of Hunter's<sup>11</sup> method which gave accurate results in the determination of iodine in material such as the thyroid gland, which contains large quantities of iodine. This method, however, is not applicable to the study of iodine in blood and tissues, unless enormous amounts of material are used. Ten years later, both von Fellenberg<sup>12</sup> and McClendon<sup>13</sup> published methods for the determination of iodine in organic material. Both these methods have led to definite advances in the knowledge of iodine metabolism, yet neither method is definitely satisfactory.

McClendon's method<sup>13</sup> is accurate but suffers from being too cumbersome for ordinary use. Most of the best studies in blood iodine

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have been made with modifications of von Fellenberg's method.<sup>12</sup> Some workers, however, consider that the results are unreliable. Others<sup>14</sup> who believe that the principles involved in von Fellenberg's method are sound, admit that there is definite need for an improvement in the procedure.

Therefore it seemed necessary to reinvestigate methods for the estimation of iodine in blood before researches in this field could progress much further.

### II. PRELIMINARY INVESTIGATION OF METHODS FOR THE DETERMINATION OF IODINE

Before attempting to devise an entirely new procedure it was deemed advisable to investigate all existing methods that seemed at all appropriate. This study was commenced in the spring of 1930. The method of von Fellenberg<sup>12</sup> and several of its modifications were carefully studied. (Aitkin,<sup>15</sup> Leitch and Henderson,<sup>17</sup> Closs,<sup>18</sup> Veil and Sturm.<sup>19</sup>)

There were two reasons why no modification of von Fellenberg's method was satisfactory and it seemed impossible to modify it in a manner to overcome these inherent difficulties. In the first place, in order to destroy organic material, von Fellenberg heats open crucibles containing the iodine to a dull red heat (i. e. at least 550° C. and probably frequently over 600° C.)

We investigated this problem carefully with the results shown in table I. Each crucible contained 100 micrograms\* of iodine in the

TABLE I  
*Heat Losses*

Test no.	Micrograms of iodine added	Substance used	Temperature	Time in minutes	Amount recovered	Per cent loss
1	100	KI	350°	30	100.4	0.4
2	100	KI	350°	30	100.8	0.8
3	100	KI	400°	30	92.7	7.3
4	100	KI	400°	30	97.2	2.8
5	100	KI	400°	30	94.0	6.0
6	100	KI	450°	30	75.6	24.4
7	100	KI	450°	30	80.6	19.4
8	100	KI	450°	30	76.6	23.3

form of potassium iodide and one c.c. of a saturated solution of sodium hydroxide. At 450° C. during one-half hour there was a 20 per cent loss of iodine and the loss was somewhat variable, possibly

\* A microgram is 1/1000 of a milligram and is frequently called a gamma.

due to differences in temperature in various parts of the oven. In the same length of time there was a definite loss even at  $400^{\circ}$  C. The thermocouple registering the oven temperature was in the hottest part of the oven and when the room was darkened none of the crucibles appeared red.

In the second place, the method of von Fellenberg and the modifications mentioned above involve a technic which most laboratory workers find extremely difficult and they usually fail to master it without several months of constant practice.

Although many workers continue to use this method and get valuable results, von Fellenberg himself apparently recognized the necessity for improvement as is manifest by his publication of a new method in 1930.<sup>20</sup>

His new procedure is more satisfactory than the older method but still is not adequate for present requirements. The material is heated to a dull glow for fifteen minutes and hence there is considerable loss of iodine. The technical difficulties of the former method are avoided to a certain extent but the procedure now requires special apparatus with which only one determination can be made at a time. This precludes its use as a routine measure in a blood chemistry laboratory.

Turner<sup>21</sup> described a colorimetric method for the determination of iodine. This method failed to give satisfactory results in the laboratories of the Cleveland Clinic and Turner<sup>22</sup> apparently experienced considerable difficulty with it, according to a later publication. Prof. E. C. Dodds<sup>23</sup> states that similar principles were employed in his laboratories in attempts to estimate iodine, but the methods failed to give satisfactory results.

In order to avoid the losses of iodine which are encountered by von Fellenberg's method, numerous authors have employed a method of closed combustion. The first method of this type that we investigated was that of Karns.<sup>24</sup> The results secured by this method are definitely too high. The inaccuracy is due to incomplete combustion of organic material. The results were so erroneous in our experience that the method had to be discarded. We considered attempting a recombustion of the material absorbed following the first incineration but this made the process so cumbersome that it did not seem desirable to attempt it.

Foster<sup>25</sup> uses Leipert's<sup>26</sup> modification of Pregel's<sup>27</sup> method and obtains satisfactory results. Metzger and Baumann<sup>28</sup> successfully use a closed combustion method. These procedures, particularly the latter, require special apparatus and for this reason were discarded. Moreover, both methods, when applied to blood, involve the slow process of drying. Therefore it seemed desirable to attempt to

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create a new and more satisfactory method for the determination of iodine in biological material. The following criteria were specified: *The method must be rapid, the results accurate, the technic not unusual and the apparatus simple.* An additional aim was to devise, if possible, a method by means of which one operator could make several determinations at one time.

The principles involved are relatively simple and have previously been applied in the Kjeldahl procedure for the determination of nitrogen. The main technical difficulty in measuring nitrogen or iodine has been the separation of an element from substances which interfere with its subsequent estimation by orthodox chemical methods. In the Kjeldahl method, nitrogen is estimated as ammonia and since it is non-volatile in acid solution but volatile from an alkaline solution, it is possible to destroy the organic matter by acid digestion and to remove the nitrogen and ammonia from the remaining mixture by alkalization, followed by distillation. The properties of iodine are just the opposite. It is non-volatile, within a limited temperature range, in alkaline solution, but can be distilled quantitatively from an aqueous acid solution. Hence it is possible to isolate iodine for estimation by alkaline digestion followed by acid distillation.

At first, in an attempt to avoid the process of alkaline digestion, we tried to liberate the iodine from the blood with sulphuric acid and hydrogen peroxide, to distill it off into a suitable absorption train and then to estimate it by one of the common chemical procedures. This attempt failed completely because large amounts of organic material were distilled off with the iodine and interfered with the subsequent steps. It was only after extensive research along these lines that we discovered that Pfeiffer<sup>29</sup> had published a report stating that he had satisfactorily perfected this procedure. Shortly after his first publication, however, Pfeiffer also discovered that the method was not practicable and published two other papers<sup>30 31</sup> in which he advised conducting the gas from the distillation flask through a combustion furnace in order to complete the destruction of organic material. If large amounts of fat are present in the specimen, the method will not give satisfactory results, and in any case it is cumbersome and requires considerable special equipment. These investigations on technic were then continued with the results shown below.

### III. A METHOD FOR THE DETERMINATION OF IODINE IN BIOLOGICAL MATERIAL

#### A. Fusion with Potassium Hydroxide

Ten cubic centimeters of blood are placed in a 250 c.c. nickel crucible together with 10 c.c. of a saturated solution of potassium

hydroxide, and are heated gently over a Bunsen flame. At first there is excessive foaming and either the burner must be manipulated under the crucible or the crucible must be manipulated over the flame. In any case, it is probably wise for the chemist to wear spectacles during this procedure, because careless manipulation may result in spattering, although this contingency is never encountered by experienced, careful workers. When the foaming abates somewhat, the organic material is washed from the sides of the crucible with a small quantity of water. The boiling is continued for a few minutes, and the walls of the crucible are washed two or three times with small quantities of water. Then the mixture is boiled until foaming ceases. This procedure requires about fifteen minutes.

The crucible is placed in a muffle furnace at  $250^{\circ}\text{C}$ . for thirty minutes. During this process, volatile and inflammable gasses are driven off. With experience, one can recognize the appearance of the fused material when this change is complete so that frequently the crucible need remain at  $250^{\circ}\text{C}$ . for not more than fifteen or twenty minutes. If the temperature is increased too soon, inflammation occurs. The temperature is increased to  $360^{\circ}\text{C}$ . and is kept there for ten minutes. Then the crucibles are removed from the oven.

#### *B. Extraction with ethyl alcohol*

Sufficient water is added to the crucible to dissolve all the easily soluble material, the lumps being broken down with a stirring rod. The water is boiled off gently, until a fluid paste is formed on cooling and stirring with the stirring rod. Twenty-five c.c. of 95 per cent alcohol are added. On stirring, the paste forms a fluid sludge which separates from the alcohol in the bottom of the crucible. Any material adhering to the sides of the crucible can be scraped down into the sludge with the stirring rod. After some minutes of stirring, the alcohol is decanted off into a 250 c.c. nickel crucible containing 1 c.c. of a saturated solution of potassium hydroxide. The sludge is then leached four more times with 10 c.c. portions of alcohol. If, during this procedure the sludge forms a thick paste, it is moistened with a few drops of water. After extracting, the sludge contains none of the iodine. The alcohol is evaporated on a steam bath and the contents of the crucible are dried gently over a free flame.

#### *C. Ashing*

The crucible is placed in a muffle furnace at  $385^{\circ}\text{C}$ . for ten minutes. A stream of oxygen (2 liters per minute) is passed through the oven during the process of ashing.



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### *D. Purification by Distillation*

The residue in the crucible is dissolved in water and filtered into a 500 c.c. Claissen flask. The distillation apparatus is arranged as indicated in Figure 1. The end of the tube leading from the con-

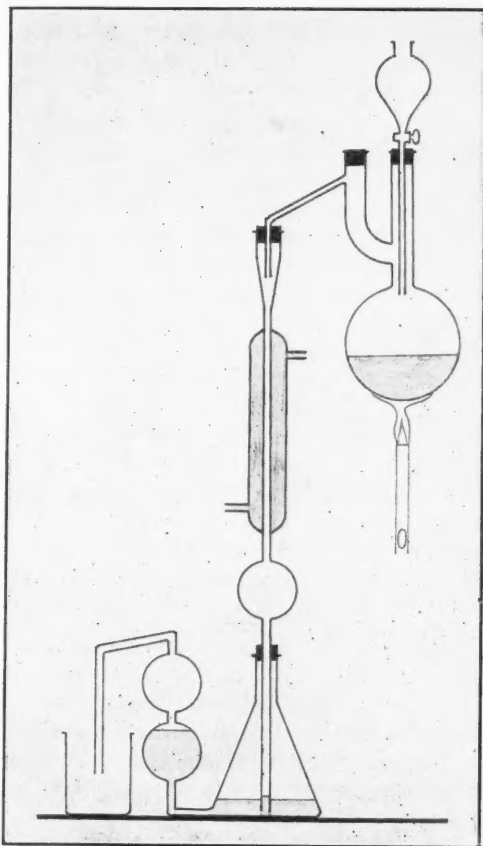


Fig. 1

denser dips under the surface of a mixture consisting of 25 c.c. of water, 0.5 c.c. of a 10 per cent solution of sodium bisulphite contained in the 250 c.c. Fresenius absorption flask. Five c.c. of a 50 per cent solution of sulphuric acid, 2 c.c. of a 10 per cent solution of ferric sulphate, and 2 c.c. of a 30 per cent solution of hydrogen peroxide are added through the dropping funnel. More acid is added if necessary to make the solution strongly acid. The presence

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or absence of ferric hydroxide acts as an indicator. The total volume of the solution at this time should be about 250 c.c. This is distilled for one-half hour with frequent additions of a 30 per cent solution of hydrogen peroxide. At the end of this step, the volume of the solution in the Claissen flask should have been reduced to about 50 c.c. Unless the distillation is carried on briskly not all the iodine will be carried over in one-half hour. The distillate is transferred to a 600 c.c. beaker.

#### E. Determination of Iodine

Carbon dioxide and sulphur dioxide are liberated from the distillate by boiling for three minutes. Immediately a 10 per cent solution of potassium hydroxide is added until the solution is alkaline to litmus paper. Not more than 1 c.c. of the potassium hydroxide should be required. The alkaline solution is then boiled and evaporated to a volume of about 10 c.c. and this is transferred to a 50 c.c. Ehrlenmeyer flask by washing the beaker three times with small quantities of iodine-free water. One drop of methyl orange is added and the solution is neutralized with a 3 per cent solution of sulphuric acid. Three drops of sulphuric acid in excess of the amount required for neutralization are added, and then one drop of bromine. Upon shaking, the solution should turn yellow immediately. Then it is evaporated to a volume of about 2 c.c. One drop of a one per cent solution of starch and a minute crystal of potassium iodide are added and titration is done with a thousandth normal solution of sodium thiosulphate. A microburette or a pipette may be used for the titration. We use a 0.2 c.c. pipette graduated in thousandths. With practice in a good light the error in titration is not more than 0.002 c.c.

#### F. Calculation

One cubic centimeter of thousandth-normal thiosulphate solution equals 21.2 micrograms of iodine.

#### G. Reagents and Their Purification

1. *Distilled Water.* Distilled water is made distinctly alkaline with potassium hydroxide and redistilled from a glass still.
2. *Potassium Hydroxide.* A saturated solution of potassium hydroxide is used, which can be purified by washing in a separatory funnel with iodine-free alcohol. It is essential that the solution of potassium hydroxide be saturated during this procedure.
3. *Iodine-free Alcohol.* Iodine-free alcohol is prepared by distilling an alkaline solution.
4. *Sulphuric acid, 50 per cent.* Iodine may be removed from sulphuric acid by heating the concentrated solution to 150° to 200°

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C. for five hours. This then is diluted 50 per cent with iodine-free water.

5. *Ferric Sulphate*. A 10 per cent solution of ferric sulphate in 1 per cent sulphuric acid is purified by boiling.

6. *Hydrogen Peroxide, 30 per cent*. Hydrogen peroxide is purified by boiling for a few minutes under reduced pressure. We have never found iodine in peroxide.

7. *Potassium hydroxide, 10 per cent solution*.

8. *Methyl orange, 1 per cent solution*.

9. *Sulphuric acid, 3 per cent solution*.

10. *Sodium Bisulphite, 10 per cent solution*. The bisulphite solution usually does not contain a sufficient amount of iodine to interfere with the method, but if necessary, it can be purified by washing the dry powder with alcohol.

11. *Bromine*. Many laboratory workers have had difficulty in the purification of this reagent, and others have ignored the large quantities of iodine which it usually contains. Iodine can be removed from bromine by the following simple procedure: 50 c.c. of bromine are placed in a retort and covered with a layer of 10 per cent copper sulphate, about 1 cm. deep. The bromine is distilled through the sulphate solution into an ice-cooled container.

12. *Sodium Thiosulphate, thousandth-normal—N/1000*. This solution should be kept away from light.

13. *Starch, 1 per cent solution*.

14. *Potassium iodide*.

### H. Discussion

The method as outlined above requires about three hours from the time the blood is taken until the results are obtained. Thus the technic is much more rapid than most of the available procedures. Several determinations can be made simultaneously by one technician. The method can be greatly simplified when used for the determination of substances containing larger amounts of iodine and less organic material.

The thiosulphate should be standardized against potassium iodate, using quantities of iodine similar to those to be estimated. The standardization should be checked every two or three days. All titrations should be done under the same conditions of light, fluid volume, temperature and acidity. Since bromine oxidizes potassium iodide with the liberation of iodine, it is wise, if possible, to carry the flask to a different room immediately after boiling off the bromine, in order to complete the procedure away from bromine fumes.

It is possible frequently to omit the alcohol extraction, the object of which is to avoid the necessity of prolonged ashing which results

in the loss of iodine. During the fusion all of the iodine in organic combination is converted to the inorganic form. If organic material is present in large quantities, as in blood, it interferes with the subsequent steps. Only a small proportion of this organic material is carried over with the alcohol.

On very rare occasions, even when the above technic is carefully followed, enough organic matter may be carried into the distillation flask to interfere seriously with the liberation of iodine. The presence of such an amount of organic material can be recognized by an unusually dark color of the solution resulting from reduction of the ferric sulphate. This difficulty can be successfully overcome by the addition of an excessive amount of a saturated solution of potassium permanganate to the hot mixture before distilling and before hydrogen peroxide is added, as this undergoes double decomposition with the permanganate.

If only a comparatively small amount of organic material is present, as in the case of diiodotyrosine or even thyroid tissue, it is possible to omit the alcoholic extraction completely.

A blank should be run on all reagents frequently, and the blank value must be subtracted each time a determination is done. Frequently this value is 0.0 and should never be more than 0.2 micrograms.

Table II presents a series of results showing the determination of

TABLE II  
*Estimation of Iodine (Whole Procedure)*

Test no.	Substance used	Micrograms of iodine added	Amount of iodine recovered	Per cent of recovery
1	KI	1.05	1.05	100
2	KI	1.05	1.05	100
3	KI	1.05	1.01	96
4	KI	1.05	1.01	96
5	KI	2.1	2.12	101
6	KI	2.1	2.14	102
7	KI	2.1	2.02	96
8	KI	2.1	2.01	96
9	KI	2.1	1.89	90
10	KI	2.1	2.08	99
11	KI	5.25	4.91	93
12	KI	5.25	5.02	95
13	KI	5.25	5.40	103
14	KI	5.25	5.06	96
15	KI	5.25	5.02	95
16	KIO <sub>3</sub>	2.1	2.03	97
17	KIO <sub>3</sub>	2.1	2.10	100
18	KIO <sub>3</sub>	2.1	2.14	102
19	KIO <sub>3</sub>	2.1	2.14	102
20	KIO <sub>3</sub>	2.1	2.14	101
21	KIO <sub>3</sub>	2.1	2.16	103
22	KIO <sub>3</sub>	2.1	2.12	101

Average recovery 98.4%

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iodine when known quantities of potassium iodide and potassium iodate were used. The average recovery of 98.4 per cent and the regularity of results is gratifying.

Table III shows a series of results obtained by using known

TABLE III  
*Estimation of Iodine (Whole Procedure)*

Test no.	Substance used	Micrograms of iodine added	Amount of iodine recovered	Per cent of recovery
1	Para-iodo-benzoic acid	.79	.77	98
2	"	.79	.73	92
3	"	.79	.79	100
4	"	3.95	3.95	100
5	"	3.95	3.84	97
6	"	3.95	3.82	97
			Average recovery	97%
7	Di-iodo-tyrosine	4.60	4.52	98
8	"	4.60	4.60	100
9	"	4.60	4.56	99
			Average recovery	99%

amounts of diiodotyrosine and paraiodo benzoic acid, which are quite comparable to those obtained by the use of inorganic compounds.

The most commonly accepted single criterion for the accuracy of a microchemical method as applied to biological material is the recovery of added quantities of the chemical in question from blood, tissue, or food. Success in this regard, as shown in Table IV, increases confidence in the procedure.

TABLE IV  
*Recovery of Iodine Added to Blood*

Test no.	Micrograms of iodine in blood	Micrograms of iodine added	Micrograms of iodine found	Micrograms added iodine recovered	Per cent added iodine recovered
1	0.79	2.1	2.81	2.02	97
2	0.79	2.1	2.71	1.92	91
3	0.79	2.1	2.71	1.92	91
4	0.79	2.1	2.85	2.06	98
5	0.79	2.1	2.81	2.02	97
6	0.71	5.25	5.84	5.13	98
7	0.71	5.25	5.75	5.04	96
8	0.71	5.25	5.48	4.77	91
				Average recovery	95%

The question of loss of iodine by evaporation has been investigated. The amount of volatilization is a function of both time and temperature. The loss in ten minutes at 385° C., in the presence of excessive quantities of potassium hydroxide, from material containing such minute quantities of iodine, is so small that its detection by chemical methods is very difficult. The loss probably never is more than 2 per cent.

Hydrogen peroxide is a particularly suitable reagent to use during the distillation procedure, since it liberates iodine from all its combinations. Iodides are quantitatively oxidized by hydrogen peroxide with the formation of free iodine. Iodates and periodates undergo double decomposition with the liberation of free iodine, and in addition the iodine in organic combination is liberated by hydrogen peroxide in strongly acid solution.

The Winkler method of titration which is used in this and several other methods is valuable but is likely to be treacherous. In this procedure iodine is oxidized to iodate which in turn is used to liberate iodine from iodide in acid solution. As a result six times the original amount of iodine is available for titration. The reaction, however, is not specific for iodine. Any substance which will liberate iodine from iodide after oxidation will yield positive results. Many organic compounds have this property. It is for this reason that some of the closed combustion methods such as that of Karns<sup>24</sup> give high results. Ferric iron will also liberate iodine from iodides and will cause erroneously high values. It is our opinion that all the modifications of von Fellenberg's<sup>12</sup> original procedure are likely to err in this regard. Distillation in glass as indicated in the method described in this report should be of great value in precluding such possibilities.

#### IV. SOME STUDIES NOW IN PROGRESS IN WHICH THE NEW METHOD HAS BEEN EMPLOYED

##### A. *The Diagnosis of Hyperthyroidism*

As the name indicates, the clinical syndrome known as hyperthyroidism is characterized chiefly by symptoms which are referable to hyperactivity of the thyroid gland. Since it is the function of this gland to produce a hormone which contains iodine, it is to be expected that the iodine content of the blood should increase together with the increase in the rate of glandular activity. That this is actually the case was observed several years ago by European workers (Holst and Lunde,<sup>32</sup> and Veil and Sturm<sup>19</sup>) and more recently in this country by Turner<sup>33</sup> and Curtis, Davis and Phillips.<sup>34</sup>

There is some question as to whether or not the level of blood iodine is always elevated in hyperthyroidism. Curtis<sup>34</sup> has stated that, "In patients suffering with diffuse hyperplastic goiter, presenting the characteristic symptoms of hyperthyroidism and with varying degrees of exophthalmos, the blood iodine is consistently elevated." Turner expressed the belief, after examining fifteen patients suffering from hyperthyroidism, that only 66 per cent show an increase in blood iodine. The level of blood iodine in relation to hyperthyroidism has been reinvestigated.



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By the examination of twenty normal persons during the winter months, the level of iodine in the blood was found to vary between 6 and 9 micrograms per 100 c.c. of whole blood. This compares favorably with the normal figure of 8.3 micrograms per 100 c.c. established by Veil.<sup>35</sup> It is generally agreed that the normal level is higher in the summer. This is in accord with our findings, although we have not yet sufficient data to establish the normal figure for summer in Cleveland. Veil's summer figure for Munich is 12.8 micrograms per 100 c.c. It is not improbable that there is some geographic difference to be found in the blood iodine level. Cleveland is in a district in which the average iodine intake is definitely low. The normal blood iodine level here may therefore be somewhat lower than in districts where iodine is plentiful. In women there is a sharp increase in the level of blood iodine during the first few days of a menstrual period. During the mid-menstrual period the normal level of blood iodine is the same in women as in men. These factors must all be taken into consideration in interpreting the results of blood iodine estimation.

Table V shows the levels of blood iodine and basal metabolic rates of patients in whom clinically typical hyperthyroidism was present.

TABLE V

*Comparison of Blood Iodine and Basal Metabolic Rate in Patients with Hyperthyroidism*

Case no.	Micrograms per 100 c.c. blood iodine	Basal metabolic rate
1	19.5	+37
2	24.2	+23
3	17.9	+4
4	24.2	+34
5	38.7	+53
6	49.8	No basal rate
7	17.9	+14
8	21.5	+57
9	11.1	+70
10	23.7	+19
11	20.9	+70
12	42.4	+58
13	25.6	+34
14	28.4	+60
15	38.9	+51
16	15.3	+22
17	21.2	+49

Most of these patients were operated upon and hyperplastic glands were found to be present. In every case there was a definite increase in blood iodine. The level of blood iodine does not appear to parallel closely the severity of symptoms. There is, however, no question

regarding its definite diagnostic value. It will be noted that in Case 9 the level of the blood iodine (11.1 micrograms per 100 c.c.) approached that of the normal which is 6 to 9 micrograms per 100 c.c. This patient had been suffering from severe attacks of hyperthyroidism for several months. In the condition of hyperthyroidism there is not only an increased level of blood iodine, but also an abnormally high excretion of this element. The excretion may be so large that the patient has a negative iodine balance. If this continues over a long period of time the individual will, obviously, become depleted of iodine. This is perhaps the explanation of the extraordinarily low level of blood iodine found in the patient mentioned.

These results are obviously in agreement with those of Curtis.<sup>34</sup> Our normal figure is slightly lower than his, but we agree with him in his statement that blood iodine is increased in hyperthyroidism. Turner's<sup>33</sup> statement that 33 per cent of patients suffering from hyperthyroidism show no increase in blood iodine may result from the fact that he employs different diagnostic criteria. It is possible, however, that his iodine determinations are in error in some cases. In this regard it is interesting to note that at one stage in his procedure the directions read as follows: "Ignite the alcohol and allow to burn until the crucible is dry. Heat the crucible over a low Bunsen flame with a to-and-fro motion, the crucible being allowed to glow to a bright red for a few seconds." In our hands both those steps resulted in a definite loss of iodine.

There is little value in a laboratory method of diagnosis if it is useful only in cases in which the clinician is capable of making a diagnosis at a glance. Nothing could be easier than the diagnosis of typical marked exophthalmic goiter. On many occasions, however, the differential diagnosis of hyperthyroidism may perplex even the most experienced and careful observer. The following four cases are exemplary of the type of diagnostic difficulty which may arise.

*Case 1.* A young woman, aged twenty-four years, complained of weakness, sweating, a persistent tachycardia and a loss of 25 pounds during the year and a half previous to her examination. The patient's basal metabolic rate had been plus 42 per cent before admission to the Clinic, and a diagnosis of hyperthyroidism had been made. We found that the blood iodine was 6.4 micrograms per 100 c.c., a low normal figure. The patient was placed in the hospital and on repeating the basal metabolic rate it was found to be only plus 7 per cent at one time and plus 3 per cent at another.

Questioning elicited the fact that the patient had been under considerable nervous strain during a long period of time and that the

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loss of weight could readily be accounted for by loss of appetite and resultant undernourishment. Her hands and feet were cold. It was the consensus of opinion of her physicians that this patient did not have hyperthyroidism but was suffering from nervous exhaustion and tachycardia of functional origin and nervous exhaustion. Infected tonsils contributed to the general condition of exhaustion.

Since no operation was performed, no pathological proof is at hand, but the final clinical diagnosis was in agreement with the results of the blood iodine determination.

*Case 2.* A man, forty-two years of age, complained of nervousness but of no loss of appetite. Hyperhidrosis was present. On examination, the pulse rate was 90; blood pressure, 200 systolic and 140 diastolic; basal metabolic rate, plus 26 per cent. The level of blood iodine was low, 5.8 micrograms per 100 c.c. For this reason, it was thought that the patient was not suffering from hyperthyroidism. In the hospital the basal metabolic rate decreased to normal within a period of two days without the use of Lugol's solution. It was agreed that the patient's symptoms could be the result of the cardiovascular condition and a diagnosis of essential hypertension was made. There was no operation.

Cases 3 and 4 are in marked contrast to the picture seen in Cases 1 and 2.

*Case 3.* A married woman, aged forty-two years, complained of enlargement of the thyroid gland, nervousness, and a throbbing heart. She had suffered from hyperthyroidism for seven years and a partial thyroidectomy had been performed at that time. The diagnosis was made difficult by the fact that the patient was gaining weight and that her basal metabolic rate was minus 12 per cent. The blood iodine was 28.3 per cent. This was an almost definite diagnostic sign of hyperthyroidism. Operation was performed and a diffuse adenomatous goiter was removed involving both lobes of the thyroid gland.

*Case 4.* A woman, thirty-three years of age, complained of nervousness and loss in weight, although she had a good appetite. Physical examination revealed that the thyroid gland was enlarged to two or three times its normal size. Exophthalmos was not present and there were no cardiovascular symptoms suggestive of hyperthyroidism. The patient's hands and feet were cold and the basal metabolic rate was minus 3 per cent. The blood iodine was 18.1 micrograms per 100 c.c. A diagnosis of hyperthyroidism was made. At operation, an adenoma of the right lobe of the thyroid gland was removed, which, microscopically, exhibited definite hypertrophy and hyperplasia.

In concluding the discussion of the diagnostic value of blood iodine in studying thyroid hyperactivity Curtis<sup>34</sup> might again be quoted. He states correctly that "the significance of the blood iodine in thyroid disease is similar to that of the blood sugar in diabetes mellitus, and to that of the blood calcium in parathyroid disease." In the case of blood iodine the significance seems even greater than that suggested by Curtis. Here, for the first time, we have an accurate chemical method for measuring the amount of a hormone in the blood stream and thus can obtain a direct measure of the rate of glandular function.

### *B. The Diagnosis of Hypothyroidism*

A sufficiently extensive study has not yet been conducted to warrant a definite conclusion concerning the diagnostic value of blood iodine studies on patients suffering from hypothyroidism. The changes certainly are not of the magnitude observed in hyperthyroidism. A considerable portion of the iodine found in normal blood is apparently in various stages of anabolism or catabolism and is not physiologically active. This portion remains moderately constant, and varies more with iodine intake than it does with thyroid activity. A limited number of results indicate that, even in patients in whom severe myxedema is present, the total blood iodine may reach the lower normal levels. Curtis, Davis and Phillips<sup>34</sup> state that in clinical hypothyroidism the blood iodine is decreased about 20 per cent below the normal level. In cases of complete extirpation of the thyroid gland the decrease is somewhat greater. Turner<sup>33</sup> found no decrease in the level of blood iodine in a number of patients suffering from hypothyroidism. It is probable that clinical signs and symptoms and the basal metabolic rate will continue to be of greater value in the diagnosis of hypothyroidism than the determination of the total iodine content of the blood. Possibly further investigation will demonstrate that certain fractions of the blood iodine contain all the thyroid hormone. These fractional analyses may solve the problem of the diagnosis of hypothyroidism.

### *C. A Study of the Iodine Content of the Blood and Spinal Fluid*

Table VI portrays the results of the analysis of the blood and spinal fluid of patients who were undergoing encephalographic studies and except in Case 8 no demonstrable disorders of the thyroid gland were present. These findings show that less than 30 per cent of the blood iodine is diffusable. In this regard it is interesting to note that nearly 70 per cent of the blood iodine is in organic combination.

# BLOOD IODINE

TABLE VI  
*Comparative Estimations of Blood Iodine and Iodine in the Spinal Fluid*

Case no.	Micrograms of iodine per 100 c.c. of blood	Micrograms of iodine per 100 c.c. of spinal fluid
1	7.5	1.3
2	8.6	3.4
3	8.3	1.7
4	5.9	3.0
5	8.3	1.2
6	7.4	1.2
7	5.5	1.3
8	11.1	4.5
9	6.3	0.8
10	8.4	2.7
11	8.4	1.0
Average	7.7	2.0

Veil and Sturm<sup>19</sup> and Holst and Lunde<sup>32</sup> have demonstrated that, when the thyroid gland becomes pathologically hyperactive, it is largely the organic iodine of blood which increases. Holst and Lunde<sup>32</sup> express the opinion that the iodine which is in combination with protein and hence is insoluble in ethyl alcohol contains the thyroid hormone. The cerebrospinal fluid is usually considered to be a true diffusate from blood. There is evidence to the contrary, but in any case the chemical examination of cerebrospinal fluid probably gives a more truthful picture of the diffusible elements of blood present under physiological conditions than does the examination of an artificial diffusate prepared under conditions which disturb all natural physical and chemical equilibria.

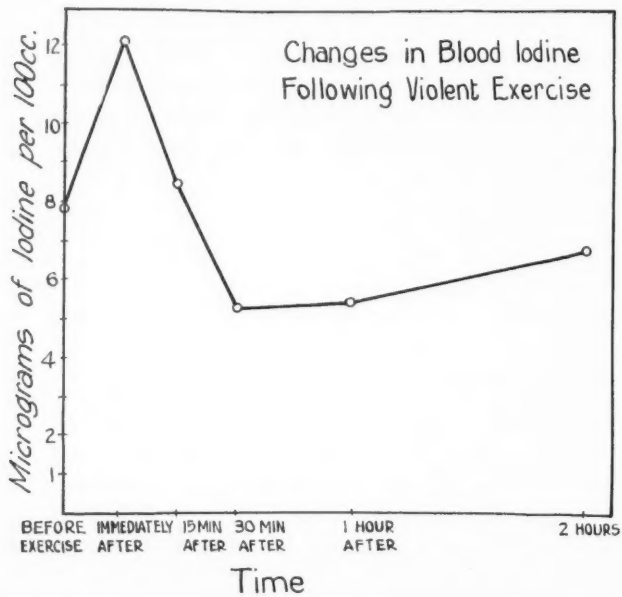
Since the spinal fluid contains but little iodine and the quantity is roughly the same as that of inorganic iodine in the blood it seems probable that no thyroid hormone is present in the spinal fluid.

It is interesting to note that Case 8 in this series was the only one in which there was a high level of blood iodine and the level of iodine in the spinal fluid is definitely the highest in the series. In this patient clinical symptoms of hyperthyroidism were present.

These results are not in agreement with those published by Hahn and Schürmeyer<sup>36</sup>, who found an average value of 10.6 micrograms per 100 c.c. of iodine in the blood and 7.4 micrograms per 100 c.c. in the cerebrospinal fluid. According to these results, 69.8 per cent of the blood iodine is diffusible. It may be that in Cologne, on account of the greater amount of iodine in the diet, there is more total and more diffusible inorganic iodine in the blood than in Cleveland. This might explain the discrepancy. The higher values might also be a result of the use of the Winkler titration which, as pointed out above, is likely to give high results in the presence of impurities.

*D. The Effect of Exercise on Blood Iodine*

The best known function of the thyroid gland is the control of the metabolic rate. For this reason changes in the blood iodine were studied when the metabolic rate was changed in persons with normal thyroid function. Severe acute infections have been shown to cause a rise in blood iodine, but in that case, although the metabolism is increased, the picture is complicated by the presence of bacterial toxins which probably act as thyroid stimulants. It was therefore decided to test the effect, in normal persons, of violent exercise on the level of blood iodine.



The subjects of the experiments were young men between the ages of 20 and 35 years. The exercise lasted for only ten minutes but was vigorous and consisted of running seven times from the ground floor to the eighth floor of a building. At the end of this period the metabolic rate was very high, in one case it was measured and found to be 353 per cent above the normal basal level.

Preliminary experiments showed that there was an immediate and sharp increase in the blood iodine. The changes are being studied in greater detail as shown in Figure 2 and Table VII. The changes in blood pressure, pulse and respiratory rate are indicative of the severity of the exertion.



## BLOOD IODINE

TABLE VII

*The Effect of Violent Exercise on the Amount of Iodine in the Blood*

Time	Blood Pressure	Pulse	Respiration	Micrograms of iodine per 100 c.c. of blood
Before	110/80	64	21	8.0
Immediately after	135/85	148	40	9.2
15 minutes after	115/82	104	23	5.3
45 minutes after	95/75	88	20	6.3
2 hours after	110/90	76	21	6.8

From these findings it is apparent that alterations in the metabolic rate occasioned by muscular activity do not bring the level of blood iodine to anything like the extreme figures observed in hyperthyroidism. This is of considerable significance in the use of the method as a diagnostic procedure, because it is frequently much more inconvenient to obtain a basal metabolic study than a sample of blood. In this regard we have also observed that blood iodine values are the same before and after eating unless the food contains large quantities of iodine. The prevalence of the use of iodized table salt makes it desirable, if possible, to obtain the blood for the iodine studies when the patient is in a fasting condition.

There is no doubt a marked increase in blood flow during periods of violent activity. This may result in a definite "flushing out" of iodine from the gland. If the entire rise in blood iodine is due to increase in blood flow through the gland one must conclude that in these experiments exercise did not act as a thyroid stimulant. During the period of fatigue which followed the exercise the iodine dropped to subnormal levels. This argues in favor of the idea that exercise and fatigue do, to some extent, alter the rate of thyroid activity.

If this is a real thyroid stimulation it is a matter of interest to see the rapidity with which the gland responds. The first sample of blood was taken immediately on the conclusion of the period of exercise and the iodine level was already elevated. The results show conclusively that the metabolic processes which occur in addition to the basal activity are not quantitatively dependent on the thyroid gland.

### *E. The Effect of Trauma on Blood Iodine*

Trauma in the form of orthodox surgical procedures acts as an astonishingly powerful thyroid stimulant. Major surgical manipulations are followed by a transient hyperactivity of the thyroid gland which develops within a few minutes and continues for a period of less than two to five days in uncomplicated cases. (Table IX.) The amount of iodine which suddenly appears in the blood

TABLE IX

*Repeated Postoperative Studies on the Amount of Iodine in the Blood*

Case no.	Preoperative Micrograms of iodine per 100 c.c. blood	Postoperative Micrograms of iodine per 100 c.c. blood	Type of Operation
1	9.1	45.6	Left adrenal denervation
		43.4	24 hours after denervation
		14.6	48 hours after denervation
		11.3	72 hours after denervation
2	14.17	42.4	Amputation of right breast
		143.1	Amputation of left breast
		6.7	48 hours after operation
		14.1	5 days after operation
3	9.2	95.2	Exploratory laparotomy
		110.0	48 hours after operation
		11.0	5 days after operation

(and therefore no doubt also in other tissues) is of such quantity that the source must surely be the thyroid gland. In none of these cases was iodine used in the operating room.

The extent of the reaction is no doubt somewhat dependent on the susceptibility of the patient to this type of stimulation. The experiments reported in Tables VII and IX do not reveal how much this factor influenced the results. It is, however, apparent from Table VIII that the increase in the level of blood iodine is a function of

TABLE VIII

*Changes in Blood Iodine Following Surgical Procedures*

Case no.	Preoperative Micrograms of iodine per 100 c.c. blood	Postoperative Micrograms of iodine per 100 c.c. blood	Type of Operation
1	9.2	23.8	Catheterization of ureters
2	6.8	23.3	Prostatectomy
3	8.9	36.4	Appendectomy
4	12.1	52.4	Left nephrectomy. D. & C.
5	7.1	61.2	Exploratory laboratory. Cecostomy
6	6.7	8.0	Encephalogram
7	15.3	43.5	Laminectomy
8	8.4	13.7	Encephalogram
9	8.3	20.5	Right adrenal denervation
10	11.9	21.6	Left adrenal denervation
11	14.3	46.3	Left adrenal denervation
12	8.4	24.2	Thyroidectomy. Excision of cyst of abdomen
13	8.3	11.1	Alcohol injection, nerve
14	6.5	6.1	Removal of cataract
15	5.9	19.5	Transurethral resection
16	22.9	45.8	Thyroidectomy
17	6.7	7.1	Hemorrhoidectomy
18	11.8	72.5	Thyroidectomy
19	8.2	10.1	Removal of cataract

## BLOOD IODINE

the severity of the surgical procedure. In cases 6 and 8 in Table VIII the increase in the quantity of iodine was not small; the operation was minor, viz., encephalography. In cases of removal of a cataract the results were similar. An alcohol injection resulted in an inconsequential thyroid stimulation. Major surgical procedures cause increases of several hundred per cent in the amount of iodine in the blood.

Clinical signs and symptoms have failed to make it apparent to most observers that the thyroid is other than a very sluggish gland. It has not been demonstrated previously that with adequate stimulation the thyroid may react almost as quickly as the central nervous system. The results shown in Table VIII demonstrate clearly that within an hour and a half after any extensive surgical trauma the blood iodine increases to levels observed only in extreme conditions of hyperthyroidism. The speed of this physiological reaction should impress the surgeon again with the necessity for careful preoperative preparation and every postoperative precaution in order to avoid that misfortune known as a "thyroid crisis." The physiological background of the "thyroid crisis" in cases of hyperthyroidism is no doubt associated with the additional strain on the gland imposed by the trauma incident to operation.

### SUMMARY

1. The technical difficulties in the study of the biochemistry of iodine are reviewed.
2. A new chemical method for the determination of iodine in biological material is presented, together with evidence for its reliability.
3. The application of chemical methods to the diagnosis of hyperthyroidism is discussed. Patients suffering from the disease exhibit an increase in the level of blood iodine. The value of this laboratory method is emphasized as an aid to differential diagnosis.
4. Spinal fluid contains about one-fourth as much iodine as blood.
5. Exercise causes small increases in the level of blood iodine which falls below normal during fatigue.
6. Surgical procedures cause marked transient thyroid stimulation roughly proportional to the extent of surgical manipulation.

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This work has been made possible by the Directors of the Cleveland Clinic and by the encouragement and co-operation of various members of the Staff, for which I express my sincere thanks.

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## SENILE TUBERCULOUS ARTHRITIS

### *Report of Two Cases*

WALLACE DUNCAN, M.D.

In 1879 Sir James Paget<sup>1</sup> said, "It is, I think, too often taken for granted that scrofula is almost exclusively a disease of the earlier part of life. Doubtless, young persons are much more often subjects of scrofula than are those of later years; but the old, i.e., people over 60, are, I believe, more often scrofulous than those between 30 and 50, and certainly are more often so than they are generally supposed to be." Although Sir James Paget was speaking in general of all extrapulmonary tuberculous disease, the statement is none the less applicable to tuberculous disease of the joints.

It is a fact that tuberculosis of the joints is found almost entirely in young people and a review of the literature on the subject leads one to believe that its occurrence in old people is indeed rare.

Whitman<sup>2</sup> reports 5,461 cases of tuberculosis of joints with only 17.5 per cent of the cases occurring in patients who were more than twenty-one years of age and in only one patient who was more than fifty years of age. In a review of 1000 cases of tuberculosis of the knee joint, he found no patients more than fifty years of age. However, in Alfer's<sup>3</sup> table of statistics compiled from records in Trendelenburg's clinic at Bonn, 966 cases of tuberculosis of the joints were reported among which there were fifty cases (5.1 per cent) in patients who were more than fifty years of age and sixteen in patients more than sixty years of age. A review of the literature since 1930 reveals only three cases of acute tuberculosis of the joints in old persons. Darling<sup>4</sup> has reported two cases in patients who were eighty-three and sixty-six years of age respectively, and Lane<sup>5</sup> reported a case of tuberculosis of the wrist in a man fifty-nine years of age. The apparent rarity of acute tuberculosis of the joints in old persons seems to justify this report of two cases seen at the Cleveland Clinic within the last three years.

The symptoms of this disease in these two patients were essentially the same as those found in younger individuals, except perhaps that all were more severe, the process being more rapidly destructive and the course of shorter duration.

*Case 1.* A white man, 69 years of age presented himself for examination on January 5, 1932, complaining of pain and swelling and stiffness in the left knee joint. He stated that two years previously he had twisted his left knee while plowing. Prior to that time he had had no joint symptoms whatever. Soon after this the knee became swollen and quite painful and remained so except for short periods when marked improvement occurred. Six months



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prior to examination the condition became rapidly worse with marked increase in the swelling of the joint and more pronounced limitation of movement. Throughout the month preceding admission, he had been totally incapacitated.

The patient was fairly well nourished. The temperature was 98.6° F., the pulse rate was 72, the blood pressure was 130 systolic, 71 diastolic. The left knee was greatly swollen, hot, and reddened and was extremely sensitive to the slightest pressure. The superficial veins over the lower third of the thigh were distended. There was apparent subluxation of the tibia upon the femur and virtually no movement could be elicited.

A roentgenogram revealed marked destruction of the inner condyle of the left femur. There was some new bone formation about the patella. The upper end of the left tibia was dislocated posteriorly.

The blood examination showed 4,220,000 red blood cells, 6,900 leukocytes and 78 per cent hemoglobin. The blood sugar was 97 mg. per 100 c.c., urea 24 mg. per 100 c.c. and the nonprotein nitrogen was 25.2 mg. per 100 c.c. Urinalysis and serologic tests revealed no abnormalities.

The patient was hospitalized and traction was applied to the left lower extremity. Forty c.c. of purulent fluid were aspirated from the affected joint. Bacteriologic examination of the fluid showed the presence of acid fast bacilli.

During the following week the patient's temperature varied from 100 to 101° F. Because of the advanced age of the patient, the pronounced degree of destruction of the knee joint, and evidences of an increasingly toxic state, continued palliative measures or arthrodesis, with the necessarily prolonged fixation in either instance, were deemed inadvisable and amputation was decided upon.

A mid-thigh amputation was performed and immediately following this, transfusion of 500 c.c. of whole blood was given. There was pronounced immediate postoperative reaction, the patient's temperature rising to 104° F. On the fourth day after operation the temperature and pulse rate returned to normal and the patient had an uneventful convalescence.

Pathologic examination gave the following findings: The knee was greatly enlarged and showed considerable peri-articular thickening and induration. Dissection of the tissues about the knee joint revealed considerably increased connective tissue with irregular sinuses extending from the synovial cavity. The synovial membrane was thickened, irregular and shaggy, and the joint cavity contained a large quantity of pinkish-gray, thick, mucoid exudate. The artic-

ular surfaces of the femur and tibia were roughened, irregular and eroded, and in some areas were covered by a thick, fibrinous exudate. Microscopic sections showed marked destruction of the cartilage with replacement by granulation tissue in which considerable caseous necrosis and numerous tubercles and giant cells were present.

*Case 2.* A white man, 71 years of age, was admitted to the hospital September 23, 1933, complaining of pain and swelling in the right knee. About three years before admission the patient had fallen, striking the knee on the floor. Immediately following the injury there occurred pain, swelling, and stiffness which lasted for three or four days. Following this the patient was able to be up and to continue his duties as a laundry superintendent, but several times during the following two years the knee had become swollen and painful following slight trauma. About a year before admission he had fallen on the knee again and since that time it had become progressively more swollen, painful and tender, until complete disability ensued several months before examination. The only other abnormal finding was a swollen, red, right testicle, which was painful.

The temperature was  $101.2^{\circ}$  F.; the pulse rate was 100; and the blood pressure was 140 systolic, 80 diastolic. The right knee was swollen until it was approximately twice its normal size. It was fluctuant, red, hot and very tender to pressure. There was almost complete limitation of movement and the knee was fixed in position of 35 degrees flexion. A draining sinus was present on the postero-lateral aspect of the upper third of the right leg.

The right testicle, epididymis and overlying scrotum were swollen, indurated, tense, red and tender and several small sinus tracts were present which opened from the inferior portion of the scrotum. Clinical diagnoses were tuberculosis of the right knee and tuberculous epididymitis.

A roentgenogram of the chest revealed no abnormalities. That of the right knee showed destruction of the joint cartilage, of the upper border of the medial side of the tibia, and of the outer border of the lateral condyle of the femur. Several small areas of hypertrophic change were present. The roentgenographic diagnosis was infectious arthritis.

Blood examination showed the red blood cells to number 4,790,000, white blood cells 22,950, with 97 per cent polymorphonuclear leukocytes, and 78 per cent hemoglobin. The blood urea was 33 mg. per 100 c.c. The Wassermann and Kahn tests were negative and urinalysis revealed no abnormalities.

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The patient was admitted to hospital where 200 c.c. of greenish yellow pus was withdrawn from the suprapatellar bursa. A pure culture of staphylococcus aureus was obtained. Traction was applied to the right lower extremity. Following the aspiration of pus from the knee joint, the patient's temperature returned to normal.

Epididymectomy and orchidectomy were advised and were performed by Dr. C. C. Higgins and at the same time incisions were made into the knee joint, and rubber tissue drains were inserted into the joint cavity. Areas of synovial membrane were excised and pathologic examination revealed the following findings: The sections showed fibro-fatty and granulation tissue, with the presence of several tubercles and giant cells in the granulation tissue. Pathologic diagnosis: Tuberculosis of the right knee joint.

Despite wide drainage of the knee joint, elevation of temperature persisted and the patient's general physical state became poor. A mid-thigh amputation with lateral flaps was performed under general anesthesia. There was very little postoperative reaction and convalescence was entirely normal. The patient was discharged on the tenth postoperative day.

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## EXPERIMENTAL MEDICINE AND ITS OPPONENTS

A strenuous campaign is being carried on in the United States against animal experimentation. Because of its great importance and value, organized medicine is protecting the interests of experimental research. The following paper was read before the Community Health Meeting under the auspices of the American College of Surgeons in Boston on October 17, 1934.

### THE RÔLE OF EXPERIMENTAL MEDICINE IN HUMAN SALVAGE

GEORGE CRILE, M.D.

Research in medicine has given us pure water to drink, a well-balanced diet, vaccination against small pox, the control of most of the infectious diseases, the prevention of goiter. It has charted the brain; it has given us thyroxin to cure the cretin; it has revealed to us the romance of the ductless glands; it has given the solace of anesthesia, the means to ease our pain, the prevention of surgical shock, the control of wound infections. It has given us blood transfusion, a cure for pernicious anemia, and a relief from diabetes. Medical research has so controlled the safety of children that women are called upon for fewer children to balance our population. It has banished the great plagues and given increased security to man and has lengthened the normal span of life.

Almost equally has medical research benefited our domestic animals, for the rarity of disease in animals is to a large extent due to scientific researches planned for the purpose of discovering the cause and method of prevention of such diseases as tuberculosis, cholera and rabies. These researches have been carried on wholly by subjecting animals to the necessary experimentation. It is apparent, therefore, that domestic animals have profited greatly by experiments made upon themselves in scientific researches.

The efforts of research workers have not only conferred benefits on every species of domestic animal as well as on man, but the research workers have often voluntarily used themselves for experiments as in the investigation of the cause of malaria and yellow fever, as a result of which these diseases are controlled. In war the research on man himself has gone on by means of man's self-inflicted wounds—eight million of which resulted in death. In the vast experience of the war, emotion, infection, starvation, cold, exhaustion and death have added much knowledge which will be of use to coming generations of man and of other species of animals.

It is to be remembered that every dose of insulin for diabetes, every dose of liver extract for anemia, every dose of thyroid hormone, every inoculation against diphtheria, scarlet fever or tetanus

## EXPERIMENTAL MEDICINE

is at the expense of some larger animal, a horse, dog or cow; that the test for the disease of the pituitary gland involves the life of a rat; that the test for tuberculosis of the kidney may involve the life of a guinea pig; that the test for pregnancy involves the life of a rabbit; that the standardization of the potency of adrenalin is at the expense of a rat or a rabbit; that our daily food involves the lives of steers, sheep, swine and fowls. In addition the horse is a faithful servant which man has tamed from the wild state.

Thus of all the animals that have served man and themselves by providing the control of their diseases and of man's diseases, a thousand mice, rats, rabbits and guinea pigs are used as compared with one dog, which is not used for food, does no work, is the only guest animal of man.

One of the great menaces to the life of the dog, a disease which has produced great distress in its slow torturous death, is rabies. This disease has now been practically eliminated as the result of experimentation upon the dog itself. The distemper also that affects so many dogs is now largely prevented and cured as the result of experimentation upon dogs by means of which the cause of distemper has been discovered and vaccines for its prevention and treatment have been developed. If the dog himself were to make a statement regarding the use of a limited number of his own kind for the discovery and the cure of a disease that menaces him, he would be just as much in favor of this practice as is the human being, for as we have already stated, human beings have sacrificed themselves in an effort to discover the causes of certain diseases and to devise methods of prevention and treatment.

The enormous number of cases of sickness and death among the two billions of human beings always present on the earth has actually contributed to the welfare of the dog and other domestic animals, for, as the result of the study of the cause of the diseases that affect human beings, the domestic animals also have benefited. The principles of surgery and preventive medicine which are applied to man are as effective when applied to dogs and cats and horses by the veterinarian as when applied to human beings. Thus the misfortunes and suffering of man have brought far more benefit to the dog than man has ever received from the use of the dog in research.

Those who are opposed to experimentation on animals, ask for insulin when they need it; demand aseptic operations; demand that typhoid fever be prevented; they demand anesthesia when their appendices are taken out; protection against blood poison; antitoxin for their diphtheria-stricken children; typhoid inoculation against typhoid fever; antitoxin against lock jaw; blood transfusion when

GEORGE CRILE

they are bleeding to death—and even ask for vaccination against disease for their lap dogs.

Even this cursory review of man's control over his destiny and the destiny of the vast numbers of domestic animals indicates a synthesis woven exclusively by the reason and the imagination of man. If we compare the lot of the fed and protected and contented domestic animals and the present day lot of civilized man with that of the unprotected animals of the past and of our forefathers, how utterly important it appears that we should not stop, but should promote to the utmost the experimental researches which result in the accumulation of the biologic laws and facts upon which our security depends.



## THE FRANK E. BUNTS EDUCATIONAL ENDOWMENT FUND

The Frank E. Bunts Educational Endowment Fund was established on December 31, 1928 in memory of Dr. Frank E. Bunts, a founder and director of the Cleveland Clinic Foundation who died in November, 1928. This fund is used for the advancement of medical and surgical education, through the purchase of books for the library of the Cleveland Clinic, and through a series of lectures each year delivered by speakers who have made outstanding contributions in the fields of medical education, practice, research and sciences related to medicine. This endowment is particularly appropriate as a memorial to Dr. Bunts inasmuch as he was greatly interested in medical education and from 1893 until his death, had served as Professor of the Principles and Practice of Surgery in the School of Medicine of Western Reserve University.

The following speakers have been brought to the Cleveland Clinic by the Frank E. Bunts Educational Endowment Fund:

Dr. Donald D. VanSlyke, Rockefeller Institute	Bright's Disease	April 26, 1932.
Professor J. B. S. Haldane, John Innes Horticultural Institute, Merton, England	Genetics and Medicine	November 28, 1932.
Dr. T. Wingate Todd, Western Reserve University	Roentgenographic Study of Human Growth	January 23, 1933.
Dr. Francis R. Packard, Editor, Annals of Medical History	Napoleon's Favorite Sur- geon	February 21, 1933.
Dr. Francis H. Herrick, Western Reserve University	The Life of the American Eagle	November 23, 1933.
Dr. Maud Slye, Cancer Laboratory Memo- rial Institute, University of Chicago	Recent Laboratory Findings Regarding Cancer	December 8, 1933.
Dr. Russell S. Ferguson, Memorial Hospital, New York City	The Specific Relations of Hormones to Cancer	January 25, 1934.
Dr. James D. Heard, University of Pittsburgh	The Art of Medicine	March 23, 1934.
Dr. Walter B. Cannon, Harvard University Medi- cal School	The Story of the Develop- ment of Our Ideas of Chemical Mediation of Nerve Impulses.	April 26, 1934.
Dr. Herbert C. Clark, Director, Gorgas Memorial Laboratory, Panama	Venomous Snakes and Snake Bite Accidents in Panama.	October 23, 1934.

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Members of the profession and the public are invited to attend these lectures.

## VENOMOUS SNAKES AND SNAKE BITE ACCIDENTS IN PANAMA\*

HERBERT C. CLARK

Director, Gorgas Memorial Laboratory, Panama, Republica de Panama

Since 1929, in association with Dr. Thomas Barbour of Harvard and other workers, I have been carrying out a census of snakes in the valleys of the Tuira, Chagres and Santa Maria rivers of Panama and on the plains east of Panama City. In these areas, a total catch of 3,457 snakes was made from January, 1929 to September, 1934. Of this number, 836 or 24.1 per cent were venomous snakes. During the capture of these snakes, no one was bitten.

According to this census, three species of Bothrops - fer de lance, hog nose viper, and horned palm viper are responsible for 83.6 per cent of hazardous snake bites. The victims of these bites can be treated with Bothropic antivenin. Other venomous snakes included in the catch were 31 bushmasters, 103 coral snakes and 3 sea snakes. The bushmaster and the coral snake rarely cause accidents, but if they do, specific antivenins are required.

Hospital and dispensary records in Panama seldom correctly reflect the true incidence of snake bite accidents for the following reasons:

1. The person who receives the bite is usually alone and is at a remote distance from medical assistance. No official report is rendered.

2. Many poisonous snake bite accidents are not followed by serious results. Most poisonous snakes are nocturnal in their habits, and most snake bite accidents occur in the daytime and are caused by a snake that is so full of food that it cannot escape the pedestrian's foot. Such a snake has emptied almost all its venom into the animal it killed for its food during the night, and therefore a non-lethal bite is delivered. From fourteen to sixteen days are required for a fer de lance to regenerate a maximum quantity of venom after swallowing a rat. This fact has been demonstrated by observations at the serpentarium.

3. The accident because of which the patient entered the hospital may not have been caused by a bite from a poisonous snake. What is thought to be a snake bite may prove to be an injury due to some other cause. I have seen two such instances in which the lesion was due to thorns.

4. Specific treatment for snake bite has been available for only

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\* Abstracted by Dr. Alexander T. Bunts from Bunts Lecture delivered October 23, 1934.

## VENOMOUS SNAKES AND SNAKE BITE ACCIDENTS

a few years, and most patients who are the victims of such accidents are taken to Indian doctors and curanderos who live nearby.

5. Most physicians find themselves confronted with two important obstacles in their efforts to cope with the few patients who report for treatment for snake bite. The patient does not know what species of snake bit him, and if by chance the snake was killed and brought in with the patient, the physician very often is unable to identify it and thus is unable to administer the specific antivenin.

The fer de lance strikes from an S-like position with the head about two or three inches above the ground. Of 104 snake bites, 83 were on the feet and ankle, or on hands and wrists, the latter being received when the patient was in a crouching position with his hands on the ground.

The anatomical distribution of 104 snake bites investigated in this survey was in the following order:

<i>Upper Extremities</i>		<i>Lower Extremities</i>	
Fingers	33	Toes	7
Hand	10	Foot	17
Wrist	5	Ankle	11
Forearm	5	Leg	12
Shoulder	1	Thigh	3
Total 54		Total 50	

The mortality from snake bite was as follows:

Year	Number of Cases Recorded	Deaths	Fatality Rate Per Cent
1927	19	1	5.26
1928	46	4	8.70
1929	39	2	5.13
Total	104	7	6.73

Injury from snake bite does not occur as often as might be expected considering the number of poisonous snakes counted in this census, and serious accidents resulting in death are rare. In fact, deaths from snake bite in Panama are almost as rare as deaths caused by lightning.

## FELLOWSHIPS IN THE CLEVELAND CLINIC FOUNDATION

Appointments to the Fellowship Staff of the Cleveland Clinic Foundation are made yearly. These Fellowships are open to men who hold a college degree, who have been graduated from an accredited medical school, and have served satisfactorily for one year as interne in an approved hospital. Appointments are offered in general surgery, internal medicine, otolaryngology, ophthalmology, pathology and roentgenology. The resident and assistant resident for the hospital are chosen from the group of Fellows.

The term of appointment is for two years. Approximately half of the time is spent in diagnostic work in the clinic and the other half in hospital work, which includes assistance at operations, and the preoperative and postoperative care of patients. The facilities of the research division also are open to the Fellows for work under supervision.

In addition to the training in the hospital and clinic, a definite course of instruction in medical subjects is provided. Each Monday night, one of a series of lectures is delivered and in these lectures an attempt is made to cover a wide range of clinical subjects. The lecturers are members of the staff of the Cleveland Clinic or physicians from outside the organization who speak by invitation. Each year four special series of lectures are included in the course. These are given each night for a week, and cover the special fields of gastroenterology, urology, cardiovascular diseases, hematology, otolaryngology, neurology, psychology and radiology. The total series comprises from 50 to 60 lectures in the current year. Each subject is covered every other year, so that during the two years' residence of any group of Fellows, the lectures are not duplicated.

The Fellows are expected to attend a weekly conference on roentgen diagnosis, a weekly medical conference, the Frank E. Bunts Educational Endowment Fund lectures, bimonthly pathology conferences, and the staff meetings. During the last year 152 such meetings were held.

Fellows are required to write a thesis during each year of their Fellowship service. This must be a report of original work or a clinical review of cases with a complete bibliography of the subject.

The Alumni Fellowship Association now numbers two hundred men.

The program of lectures listed on the following page is that being given during the present year, 1934-1935.

## FELLOWSHIP LECTURES

### FELLOWSHIP LECTURES

1934-1935

Oct. 8	Dr. W. E. Lower	General Management of Surgical Cases
Oct. 15	Dr. E. P. McCullagh	Present Status of Diseases of the Pituitary Gland
Oct. 22	Dr. T. E. Jones	Diagnosis of Pelvic Lesions
Oct. 29	Dr. R. H. McDonald	Differential Diagnosis and Treatment of Pneumonia

#### SPECIAL COURSE IN GASTRO-ENTEROLOGY

Nov. 5	Dr. E. N. Collins	Diagnosis of Lesions in the Stomach and Duodenum
Nov. 6	Dr. E. N. Collins	Diagnosis of Lesions in the Gallbladder and Small Intestine
Nov. 7	Dr. E. N. Collins	X-ray Findings in the Colon
Nov. 8	Dr. C. L. Hartsock	Duodenal and Gastric Ulcer
Nov. 9	Dr. John Tucker	Types of Colitis and Their Treatment
Nov. 12	Dr. Howard Dittrick	Historical Medicine (Gallery Talk—Cleveland Medical Library)
Nov. 19	Dr. C. C. Higgins	Diagnosis and Treatment of Urinary Calculi
Nov. 26	Dr. R. L. Haden	Technique of a Blood Examination
Nov. 27	Dr. R. L. Haden	Classification and Treatment of Anemias
Dec. 3	Dr. M. A. Blankenhorn	Clinical Significance of the Diaphragm

#### SPECIAL COURSE IN CARDIOVASCULAR DISEASES

Dec. 10	Dr. R. W. Scott	Aortitis
Dec. 11	Dr. A. C. Ernstene	Rheumatic Heart Disease and Subacute Bacterial Endocarditis
Dec. 12	Dr. A. C. Ernstene	Angina Pectoris and Coronary Occlusion
Dec. 13	Dr. A. C. Ernstene	Clinical Electrocardiography and Cardiac Arrhythmias
Dec. 14	Dr. A. C. Ernstene	Treatment of Heart Disease
Dec. 17	Dr. W. J. Engel	Obstructive Lesions of the Genito-Urinary Tract

#### SPECIAL COURSE IN NEUROLOGY

Jan. 7	Dr. L. J. Karnosh	Diseases of the Peripheral Nerves The Clinical Interpretation of Pain
Jan. 8	Dr. L. J. Karnosh	Diseases of the Spinal Cord Toxic Cord Diseases
Jan. 9	Dr. L. J. Karnosh	Disorders of the Brain Stem The Neuro-hypophyseal Syndromes
Jan. 14	Dr. L. J. Karnosh	Disease of the Extra-pyramidal Systems The Chorea and Dystonias
Jan. 15	Dr. L. J. Karnosh	The Encephalitides Encephalomyelitis disseminata
Jan. 16	Dr. L. J. Karnosh	Modern Problems in Neurology
Jan. 21	Dr. Allen Graham	Diseases of the Thyroid Gland
Jan. 22	Dr. Allen Graham	Diseases of the Thyroid Gland

## FELLOWSHIP LECTURES

Jan.	28	Dr. T. E. Jones	Malignancies of the Face and Mouth
Feb.	4	Dr. B. H. Nichols	Tumors of the Lungs
Feb.	5	Dr. B. H. Nichols	Pulmonary Infections
Feb.	11	Dr. D. R. McCullagh	Recent Advances in the Chemistry of Hormones

### SPECIAL COURSES IN DISEASES OF THE EAR, NOSE AND THROAT

Feb.	18	Dr. C. E. Pitkin	Foreign Bodies in the Respiratory Tract and Esophagus
Feb.	19	Dr. J. M. Waugh	Lesions of the Esophagus
Feb.	20	Dr. Wm. V. Mullin	Clinical Significance and Complications of Sinus Disease
Feb.	21	Dr. Wm. V. Mullin	Diagnosis and Treatment of Diseases of the Nose and Throat
Feb.	22	Dr. W. L. Deeton	Ear Disease
Feb.	25	Dr. Otto Glasser	Physical Foundations of Radiology
Feb.	26	Dr. E. P. McCullagh	Management of Diabetes
March	4	Dr. W. J. Gardner	Surgical Management of Non-Tumorous Intra-Cranial Lesions
March	5	Dr. W. J. Gardner	Surgical Management of Brain Tumors
March	11	Dr. J. A. Dickson	Management of Tuberculosis of the Joints
March	18	Dr. E. W. Netherton	Diagnosis of Common Skin Diseases
March	19	Dr. E. W. Netherton	Treatment of Common Skin Diseases
March	25	Dr. U. V. Portmann	Radiosensitivity of Tumors
April	1	Dr. R. L. Haden	Chronic Arthritis From a Medical Standpoint
April	2	Dr. W. S. Duncan	Chronic Arthritis From a Orthopaedic Standpoint
April	3	Dr. W. S. Duncan	Low Back Pain
April	8	Dr. George Crile	Crises and Emergencies of Surgery
April	15	Dr. A. D. Ruedemann	Headaches of Ocular Origin
April	16	Dr. A. D. Ruedemann	Lesions Which Can Be Diagnosed by Examination of the Fundus
April	22	Dr. D. R. McCullagh	Physiology of the Prostate
April	29	Dr. A. T. Bunts	Spinal Cord Lesions
April	30	Dr. A. T. Bunts	Surgery of the Autonomic Nervous System
May	6	Dr. R. L. Haden	Diseases of the Spleen in Relation to Diseases of the Blood
May	7	Dr. Otto Glasser	Radiation From Living Tissues
May	13	Dr. I. M. Hinnant	Role of Allergy in General Medicine
May	14	Dr. I. M. Hinnant	Treatment of Hay Fever
May	20	Dr. W. E. Lower	Malignancies of the Urinary Tract
May	27	Dr. U. V. Portmann	Roentgen Ray Therapy of Non-Malignant Disease



## HUNNER ULCER OF THE BLADDER\*

### A REPORT OF FORTY-FIVE CASES

J. E. YOUNG, JR., M.D., *Fellow in Surgery*

In 1836, Mercier first called attention to ulcerations which develop in the floor of the loculate bladder, and similar cases were reported by Tait in 1870. In 1900, Fenwick compared chronic, solitary simple ulcer of the bladder with ulcer of the stomach but Rakitansky and Tait previously had made this comparison. In 1914, Hunner reported eight cases of "a rare type of bladder ulcer in women." He described the symptoms and the pathologic appearance of the lesion and suggested that pericystitis might be the cause of a primary lesion of which the bladder ulcer was a secondary manifestation. Other cases have been reported by Nitze, Kretschmer, Bumpus and Meisser, Hinman, Furness, Keene, Peterson and Hager, Folsom, Higgins, Eisenstaedt and McDougall, and Meads.

Various authors have referred to this clinical entity described by Hunner and designated by many as Hunner ulcer of the bladder, as interstitial cystitis, elusive ulcer, pan-mural cystitis and submucous fibrosis.

*Etiology:* Besides having been the first clearly to define this lesion, Hunner was also the first to recognize a possible relationship between focal infection and the ulcer. It is now a generally accepted fact that infection in the teeth, tonsils, adenoids or nasal sinuses may be carried to the bladder by the hematogenous route. In 1931, Meisser and Bumpus added further proof to the theory that infection is an etiologic factor when, by experimental research, they demonstrated that certain streptococci which were present in various foci of infection had a selective affinity for the urinary tract and produced submucous ulcers and other infections of the urinary bladder. Kretschmer, however, found no infection present in the cervixes or adnexae, and in his fourteen cases of elusive ulcer of the bladder he consequently disclaimed the theory that the disease should occur more frequently in women because of pelvic infections. Keene, after eradicating all foci of infection in his twenty-five cases, suggested that these ulcers might be due to a hematogenous infection or that they might be secondary to an inflammatory non-tuberculous lesion in the upper urinary tract. In this series, foci of infection were present in twenty-nine cases.

*Incidence:* Hunner stressed the fact that this disease occurs more frequently in women than in men, and this has been verified by most writers on the subject. In our series, forty-one cases occurred

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\* Abstracted by Dr. C. C. Higgins from a thesis submitted to the Fellowship Committee.

in women and four in men. The youngest patient was eighteen years of age, the oldest seventy-seven. The average age of these patients was forty-eight years.

*Symptoms:* Both diurnal and nocturnal frequency of urination is the complaint first mentioned by the majority of patients suffering from Hunner ulcer of the bladder, and this frequency is almost clocklike in regularity according to the experience of Furness. Forty-two of our 45 patients mentioned this symptom. Pain is the next most frequently mentioned symptom and it usually occurs in the suprapubic region. It is experienced, in most instances, when the bladder is distended and generally it can be reproduced by touching the lesion with the tip of the ureteral catheter. The most usual combination of symptoms in our series was frequency accompanied by dysuria and suprapubic pain. The pain was present in one or both sides of the lower abdomen, one or both thighs, the vagina, the rectum, the back and the perineum. Other urinary symptoms which are found occasionally are hematuria, urgency, burning and tenderness. Backache and symptoms referable to the gastro-intestinal tract were frequently mentioned. In six of these cases there was aggravation of the symptoms referable to the bladder before menstruation.

The average duration of symptoms in these cases was four and one-half years; the shortest duration was one month and the longest twenty years.

The urine is clear and sparkling in the majority of cases and this was true in thirty-three of the cases in this series. Occasionally a few red and white cells are present.

*Diagnosis* usually is made by presumptive evidence secured by a carefully elicited history and by cystoscopic examination. Because of the reduced capacity of the bladder which often is only 60 or 90 c.c., the characteristic appearance of the lesion may not be recognized. Usually the ulcers are small; they may be multiple and they are found most frequently in the apex or dome of the bladder. In this series of cases, the lesion was single in thirty-one instances and multiple in fourteen. Usually the ulcer is seen to be more or less circular in form, but occasionally it may be linear, as the result of overdistention of the bladder, with a resultant cracking of the mucosa over the rigid area of the localized intramural cystitis. In cases, in which the lesion tends to be circumscribed, there is little or no increased thickening of the bladder wall at the point of involvement. If, however, the inflammatory process has extended into all the coats of the bladder and the muscularis has been invaded, there may be considerable thickening at the site of the lesion. The bases

## HUNNER ULCER

of the ulcers are quite red and at times they have the appearance of having little bubbles of air attached to them. They may be covered by a small number of fibers and occasionally small blood vessels may radiate from the ulcer. According to Higgins they frequently have the appearance of a strawberry which has been crushed against the bladder wall.

*Differential diagnosis:* The differential diagnosis usually is not difficult. The lesion may be confused with a simple ulceration or an ulceration of tuberculous origin, especially if the objective urinary findings are not distinctive. A simple ulcer rarely is found in the bladder and tuberculosis and malignancy should be considered before such a diagnosis is made. General examination and serologic studies should always be made to determine whether or not syphilis may be present. Other conditions which should be considered before making a diagnosis are chronic cystitis, bladder inflammation associated with bullous edema, and lesions due to the application of radium to malignant conditions of the vagina and cervix.

*Treatment and results:* For years there has been considerable discussion regarding the most satisfactory method of treating Hunner ulcer of the bladder. In all cases at the Cleveland Clinic a diligent search for foci of infection is instituted and such foci are eradicated when found. In twenty-nine cases, foci of infection were found in the teeth and tonsils, and a dormant renal infection was present in twelve cases.

Many writers advocate a wide resection of the ulcer including a considerable portion of the bladder. Others, however, have abandoned excision of the ulcer and now use electro-coagulation which, in some instances, has yielded remarkable results. Other methods of treatment which have been reported are periodic over-distention of the bladder, transurethral electrocoagulation, presacral nerve resection in selected cases, and transplantation of the ureters into the rectosigmoid with cystectomy. Most writers now agree, however, that conservative methods of treatment such as eradication of infection, bladder irrigation, overdistention of the bladder or electro-coagulation should be employed first.

Fulguration which usually was done under anesthesia was the method of treatment in thirty-six cases in this series. Of these thirty-six cases, nine were definitely cured, seventeen were relieved temporarily or improved, four became worse and radical procedures were advised, and six patients failed to return for further observation or treatment. In all these cases, this treatment was preceded by one or more irrigations of the bladder to determine whether irrigation was of any value in each individual case. Of three patients

treated with irrigation and overdistention, a cure was effected in one instance while one patient became worse and the other received no relief. In six cases unsatisfactory results were noted after the use of irrigation with silver nitrate solution.

Two patients were completely cured after the eradication of chronic prostatitis. Only slight temporary relief was noted by one patient after treatment with ultra-violet light which was applied directly by means of a quartz tube conductor. One patient was cured after the instillation of gomenol and argyrol.

Radical treatment was instituted in the remaining five cases. In three instances a resection of the involved area of the bladder was performed and the patients remained free from symptoms for a period of over two years. However, they then complained of some bladder discomfort which disappeared after irrigations. In two cases in which a resection of the presacral nerve had been performed previously without relief of symptoms, the ureters were transplanted into the rectum and a cystectomy was performed with complete relief of symptoms.

#### SUMMARY AND CONCLUSIONS

1. Hunner ulcer of the bladder occurs more frequently in women than in men. In ninety per cent of a series of forty-five cases in the Cleveland Clinic the disease occurred in women.

2. The disease occurs most frequently in late middle life. The majority of patients seen in this series were in the fifth decade of life.

3. Focal infection is an important etiologic factor. All foci of infection should be eliminated as a routine procedure in the treatment of this disease.

4. Diurnal and nocturnal frequency of urination associated with dysuria and suprapubic pain constitute a combination of symptoms found in over 90 per cent of the cases.

5. Hunner ulcer usually produces a diminished capacity of the bladder. The average bladder capacity in this series of cases was 135 c.c.

6. Single lesions of the bladder were seen more frequently than multiple lesions in this series of cases. (69 per cent were single; 31 per cent were multiple).

7. Conservative treatment is the method of choice which should be followed by a radical operation only as a last resort.

### STAFF MEETINGS

Staff meetings are held semi-monthly on Wednesday evenings at 7:15 P.M. Members of the profession are cordially invited to attend these meetings.

First on the program is the pathology conference at which interesting cases seen recently in the Clinic are presented and discussed. Case reports are given by the members of the fellowship staff and papers on clinical and research subjects are presented by members of the permanent staff or by physicians from outside the organization who speak by invitation. The program of these papers for the first quarter of the year is listed below.

### PROGRAM

January	2	Roentgenologic Aspects of Bone and Joint Diseases	Dr. B. H. Nichols
January	16	The Sedimentation Rate of Red Blood Cells	Dr. A. C. Ernstene
January	30	The Diagnosis and Treatment of Diseases of the Sacroiliac Joint	Dr. Wallace Duncan
February	13	Classification and Prognosis of Carcinomata of the Breast	Dr. Allen Graham
March	6	Hygiene of the Community	Dr. Harold K. Knapp, City Health Commissioner, City of Cleveland.
March	20	Cleveland Neurological Society	
March	27	Pneumothorax	Dr. R. C. McKay City Hospital Cleveland, Ohio.
April	10	The Control of Benign Prostatic Hypertrophy	Dr. William E. Lower and Dr. D. Roy McCullagh
April	24	The History and Treatment of Foot Disabilities	Dr. James A. Dickson
May	8	To be Announced	
May	22	Surgical Vascular Lesions of the Brain	Dr. James A. Gardner

## ACUTE MYELOBLASTIC LEUKEMIA\*

CLINICAL AND PATHOLOGIC REPORT OF A CASE

ALLEN GRAHAM, M.D.

The patient, an unmarried white woman, 47 years of age, was brought to the hospital in an ambulance. Her chief complaint was pain in the abdomen. Two weeks previous to this examination, while walking, she had fallen on her back and after this she had become nauseated, faint and had suffered from intense cramplike pains across the upper part of the abdomen. The symptoms persisted, but she was able to continue her duties as a social worker until one week before admission to the hospital. Since that time she had been confined to bed. The abdomen became distended and tender, she had some fever and two days prior to admission she became jaundiced. She was constipated and strong cathartics had been required. The color of the urine was darker than usual.

In addition to the usual diseases of childhood, the patient had had influenza in 1918, and scarlet fever in 1926, which had been complicated by peri-arthritis of the knees and by nephritis. A tonsillectomy had been performed in 1928.

*Examination:* On admission to the hospital, the patient's temperature was 101° F., pulse rate 126, respiratory rate 20, blood pressure, 148 systolic, 74 diastolic. The patient appeared to be well developed and nourished; she was uncomfortable and seemed to be in a state of toxemia. The skin and sclerae were icteric. There were some discolorations, swelling and tenderness about the left ankle and there was tenderness over the region of the right kidney. Adenomata were palpable in the right lobe and in the isthmus of the thyroid gland. The lungs were resonant throughout and a few moist râles were present posteriorly over the base of the right lung. The heart was slightly enlarged; the sounds were clear, regular, distinct and of good quality. A soft blowing systolic murmur was audible over the apex and was not transmitted. The second aortic sound was accentuated. The peripheral vessels were normal. The abdomen was rotund and markedly distended. The liver was markedly enlarged; it had a smooth edge, was tense and tender and extended downward to a point two inches above the right iliac crest. No other tumor masses were palpable and no fluid wave was elicited.

The tentative diagnoses were hepatic abscess following hemorrhage into the liver; chronic glomerular nephritis; adenomatous goiter; contusion and strain of the left ankle.

\* Pathology Conference preceding a Staff Meeting.



## ACUTE MYELOBLASTIC LEUKEMIA

A routine examination of the blood gave the following findings: Red cells, 4,890,000; white cells, 17,600. The differential count showed 57 per cent myeloblasts.

The clinical diagnosis was myeloblastic leukemia.

In addition to the laboratory findings shown in Table 1, there was a marked diminution in blood platelets; the coagulation time of the blood was fourteen minutes; the bleeding time was ten minutes. There was no retraction of the clot. Roentgenograms of the spine and genito-urinary tract showed no abnormalities. A blood culture was negative. The carbon dioxide capacity was normal. The urea clearance test showed some impairment of renal excretion.

Three days after the patient was admitted to the hospital, the spleen became palpable and was estimated to be four times its normal size. Areas of ecchymosis and petechial spots appeared over the entire body and slight bleeding occurred in the mucous membrane of the nose and throat. The spleen continued to enlarge, the leukocyte count continued to rise as shown in the table, and the number of erythrocytes decreased.

On the ninth day after admission to the hospital, the patient died suddenly. Death was attributed to embolus or hemorrhage into some vital center.

Necropsy was performed one hour after death.

### POSTMORTEM EXAMINATION

*General description:* The body was that of an adult, white woman, aged 47 years; it was well developed and well nourished; the weight was approximately 140 pounds and the body length was 162 centimeters. No rigidity was present. There was fairly marked lividity of the dependent parts, face, ears and upper parts of the chest, but there was no cyanosis or edema. The skin had a slight lemon tint. Petechial hemorrhages were present over the shoulders, thorax, abdomen and thighs. The hair was sparse and gray. The eyes were gray; the pupils were equal, regular, centric, dilated, and measured 6 mm. External examination of the ears and nose showed no abnormality. All the teeth had been removed and upper and lower dentures were present. The mucous membrane of the mouth showed no hemorrhages. No glands were palpable in the neck. The thyroid was irregularly enlarged; the right lobe was nodular and larger than the left. The chest was normal in shape and contour; resonance was not decreased. The breasts were small. The abdomen was distended but not rigid. A palpable mass was present in the right upper quadrant of the abdomen. A large, purplish colored, sub-

cutaneous hemorrhage was present in the right groin. Multiple hemorrhagic spots were apparent in the skin over both upper arms. Subcutaneous hemorrhages were the only abnormal findings on the extremities.

*Incision:* A semilunar incision was made joining both axillae and extending downward over the xyphoid process. A second midline incision joined this and extended to the symphysis pubis.

*Abdomen:* The subcutaneous fat was deep yellow in color; it measured 3 cm. in thickness and was dry. In the peritoneal cavity, the omentum extended over the small intestine and contained a moderate amount of deep yellow fat. The peritoneum was smooth and glistening. The liver was greatly enlarged and extended 12 cm. below the costal margin in the right mammary line, 14 cm. below the costal margin in the midline and 8 cm. below the left costal margin in the left mammary line. The dome of the diaphragm extended to the third vertebral space on the right side and the fourth rib on the left side. The contents of the upper abdominal cavity were displaced downward by the enlarged liver so that the lower pole of each kidney lay at the level of the brim of the pelvis. The stomach also was displaced downward. Otherwise the organs of the peritoneal cavity were in their normal positions. There were many enlarged, soft, yellowish-white lymph nodes surrounding the abdominal aorta.

*Thorax:* The right lung was firmly adherent to the thoracic wall by firm, old, fibrous adhesions and the right pleural cavity was completely obliterated. The left lung contained a few old, firm, fibrous adhesions at the apex and in the posterior portion. The heart was not enlarged and was free in its pericardiac sac.

The thyroid gland was almost entirely removed.

Portions of the lumbar vertebrae and the right tibia were removed for bone marrow examination.

*Lungs:* The right lung weighed 330 grams and measured 19x8x8 cm. It was composed of two lobes which were separated by a fairly deep interlobar sinus which contained numerous, old, fibrous adhesions. The pleura over the lung was thickened, most of the thickening being anterolateral; it was shaggy and grayish-white. A layer of brownish clotted blood was present on the lateral aspect of the upper lobe of the lungs. The lung was somewhat deflated; it was steel gray and had a moderate amount of anthracotic pigmentation and there were crepitations throughout. The hilar blood vessels were patent and clear and the pulmonary artery showed thickening of its wall and irregular areas of atheromatous change were present in its intimal coat. The bronchi were patent, they contained a small amount of mucoid exudate and there were a few fine, brown-

## ACUTE MYELOBLASTIC LEUKEMIA

ish-red areas which suggested the presence of petechial hemorrhages in the mucous membrane. The hilar lymph nodes were somewhat enlarged and showed marked anthracotic pigmentation; they were soft and elastic for the most part, but a few showed calcified centers. Section of the upper lobe showed a dry, pinkish-gray cut lung surface with no areas of degeneration due to pneumonia or neoplasm. The marginal areas revealed slight emphysema and at the apex there were areas of brownish discoloration in that portion of the lung which was in apposition to the clotted blood on the pleural surface. Section of the upper portion of the lower lobe of the lung beneath an area of thickened pleura showed pinkish-red, firm lung tissue which contained no air and was surrounded by a zone of brownish discolored lung tissue. Section of the remaining portion of the lobe showed a pinkish-red cut surface with scattered, small, irregular areas of petechial hemorrhage. In the lower portion of the lobe, in comparison with the diaphragmatic surface, the lung was more firm, was deeper red in color and contained no air.

The left lung weighed 300 grams and measured 20x8x9 cm. It was composed of two lobes which were separated by a shallow interlobar sinus. The pleura was thin, transparent and glistening except for the presence of a few old, fibrous tags at the posterior portion of the apex. It was steel gray and irregular; blotchy areas of anthracotic pigmentation were present which were associated with numerous small purplish-red spots, particularly on the lateral aspect of the upper lobe and along the lower margin of the lower lobe. There was a moderate amount of marginal emphysema. The lung contained air throughout except beneath the purplish-red discolorations and in the posterior portion of the inferior lobe where it had a rubbery-consistency and did not contain air. The hilar blood vessels were patent, clear, and somewhat dilated. The intimal coat of the pulmonary artery showed irregular, yellowish thickening. The bronchus was patent and there were a few, small, petechial hemorrhages in the mucous membrane and a small amount of glary mucoid exudate on its surface. The hilar lymph nodes were enlarged; they were grayish-black but were elastic and showed no calcification. Section of the upper lobe showed a pinkish-red cut surface with hemorrhagic discoloration of the marginal areas and a few small pinkish-red petechial hemorrhages throughout the lung substance itself. Section of the upper portion of the lower lobe revealed whitish-gray lung tissue with a few small, brown pigmented areas. Section of the lower portion of the lobe showed a grayish-red, firm substance containing no air. Throughout the lower portion of the lobe there were larger, blotchy, pinkish-red areas. The marginal

tissue in this portion of the lobe was collapsed.

*Heart:* The heart weighed 350 grams. It was not enlarged and measured 12 cm. from apex to base. The apex was sharp and it was made up of the musculature of the left ventricle. The epicardium was thickened, pearly gray, less transparent than normal and had brownish pigmented areas scattered over it. The coronary vessels were visible as fine, tortuous, whitish-gray ridges coursing over the surface of the heart. There was only a moderate amount of subepicardial fat. The cavities of the heart were not dilated. The endocardium was slightly thickened and less transparent than normal. The foramen ovale was closed. Few abnormalities were seen in the pulmonary and tricuspid valves. The margins of the mitral valve which were moderately distorted were somewhat thickened. The aortic valve cusps were thick and disclosed some atheromatous degeneration, particularly about their attachment in the sinuses of Valsalva and the adjacent portion of the aortic ring. The valve rings measured: tricuspid, 11 cm., pulmonary, 6 cm., mitral, 8 cm., and aortic, 7 cm. The chordae tendineae were thin and web-like in the right ventricle and were somewhat thickened and hyalinized in the left ventricle. The papillary muscles showed some hypertrophy in the left ventricle. The columnae carnae were poorly developed in the left ventricle. The myocardium was softer than normal and measured 0.3 cm. in thickness in the right ventricle and from 1.5 to 2 cm. in thickness in the left ventricle. It was soft, friable and pale yellowish-brown with darker, blotchy, deeper reddish-brown areas scattered throughout. The intimal surface of the pulmonary artery was smooth and glistening. The aorta was somewhat thickened; it showed yellowish plaques in its intimal coat and a few areas of brownish discoloration. The coronary orifices were patent and they showed a small amount of atheromatous change but the lumen was not narrowed. The right coronary artery was considerably smaller than the left.

*Liver:* The liver weighed 3600 grams. The right lobe measured 29x17x9 cm. and the left lobe measured 22x10x7 cm. It was greatly enlarged, its capsule was irregularly thickened and there was a constriction across the central portion of the right lobe. Over this constriction, the capsule was very thick, opaque and yellowish-white. The liver was grayish-brown with irregular, lighter colored areas on its surface that were raised slightly above its general contour and varied from 1 mm. to 1 cm. in diameter. These slightly elevated areas were firmer than the surrounding liver substance. The anterior margin was rounded, the liver was very much firmer than normal and on section showed a greenish-brown colored

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cut surface with indistinct lobular markings, with darker colored peripheral zones and paler areas around the central veins of the lobules. There were non-encapsulated, yellowish-white, glistening, homogeneous areas scattered throughout the liver, varying from 2 mm. to 1 cm. in diameter. In some areas the structure of the liver was almost completely replaced by pale yellowish-white tissue which corresponded with the lobular arrangement of the liver substance but which had a waxy, glistening appearance. The inferior vena cava, portal vein and hepatic vein were patent.

The gallbladder contained about 25 c.c. of glistening, glary bile. Its wall was not thickened and its mucous membrane was intact. There were no stones present. The cystic duct and hepatic duct were patent.

The glands about the gastrohepatic ligament were greatly enlarged, soft and friable. The hepatic duct was patent.

*Pancreas:* The pancreas weighed 100 grams. It measured 17x4x1 cm. Its capsule was edematous and somewhat thicker than normal. There were many enlarged lymph nodes about the head of the pancreas. On section, it was yellowish-brown, fairly uniform in appearance and showed no areas of inflammation or any tumor mass.

*Spleen:* The spleen weighed 800 grams and measured 19x12x7 cm. It was regular in outline, normal in contour but was greatly enlarged. Its capsule was purplish-gray, slightly wrinkled and had a few small, depressed, scarified areas. On section, it was deep, purplish-red, homogeneous, and was scattered with fine, whitish colored spots. There was marked hyperplasia of the splenic pulp.

*Kidneys:* The left kidney weighed 270 grams and measured 13x5x4 cm. It was irregular in outline and the posterior aspect was greatly distorted. The capsule was pearly gray, somewhat thicker than normal but stripped fairly readily, leaving a smooth, pale yellowish-brown kidney substance. The distorted posterior half of the kidney showed an irregular scar that involved the middle and inferior pole. The scarred, depressed area was yellowish-brown and multiple, fine, petechial hemorrhages were scattered over it. Section of the kidney substance revealed slight bulging and the cortex had a fine, granular appearance. It was pale, yellowish-brown with a sprinkling of lighter yellow areas which were present particularly about the medullary tissue where it was in apposition to the cortex. The medullary tissue contained purplish-brown streaks which were suggestive of petechial hemorrhages. The pelvis was not dilated but was somewhat distorted by the scarring of the kidney. Its mucous membrane was finely irregular and had fine, brownish col-

ored hemorrhagic spots. There were no areas of ulceration or scarring.

The right kidney weighed 307 grams and measured 15x8x4 cm. It was regular in outline, its shape was normal and it was somewhat enlarged. Its capsule was thickened, pearly gray, less transparent but stripped fairly readily leaving a pale yellowish-brown, smooth surface which had a scattering of fine, lighter colored pin-point spots. The kidney substance bulged slightly above the cut margin, and showed similar, paler zones about the medullary substance. The cortex had a finely granular appearance and was fairly well differentiated from the medulla. Petechial hemorrhages were seen in the medullary portion and in the mucous membrane of the pelvis of the kidney. The pelvis was not dilated and the mucous membrane, apart from the hemorrhages, showed nothing abnormal.

*Bladder:* The bladder was empty and the wall was somewhat thickened. There was no evidence of cystitis. The mucous membrane was irregularly rugated and showed no areas of ulceration or scarring.

*Genital organs:* The uterus measured 5.5x3x2 cm. It was small and atrophic and contained a rounded, pedunculated fibroid tumor 4 cm. in diameter which was attached to the fundus by a narrow pedicle. Protruding from the right anterolateral aspect of the uterus, near the fundus, was another rounded tumor mass measuring 3 cm. in diameter. The uterine wall was 1 cm. in thickness. The endometrium was smooth and regular and the cervix contained a large quantity of white, thick, mucoid secretion. There were a few cysts in the cervix. The cavity of the uterus measured 2x1.5 cm.

Each of the ovaries was 2.5 cm. in length and each measured 1.5 cm. transversely. They were yellowish-white and irregularly scarred. The ovarian tubes appeared normal.

*Adrenals:* The right adrenal gland weighed 9 grams and measured 6x2.5x1 cm. The left adrenal weighed 8 grams and measured 6x2x1 cm. They were yellowish-brown with lighter yellow spots, were uniformly firm in consistency and on section showed fairly deeply pigmented, narrowed, cortical substance with considerably more medullary tissue than normal.

*Thyroid:* Examination of the thyroid revealed a thickened, pearly gray capsule, extremely firm in consistency, which was nodular and on section showed a greatly increased stroma separating partially encapsulated early adenomata. In some of these early adenomata marked recent hemorrhage was present.

*Gastro-intestinal tract:* The stomach was small and contracted



## ACUTE MYELOBLASTIC LEUKEMIA

and contained a small amount of mucoid brownish material. The serous surface was smooth. The mucous membrane was edematous and covered by a mucoid exudate. The pyloric ring was not hypertrophied and there were no areas of ulceration or scarring. The mucous membrane of the duodenum showed irregular, fine, small swellings, but no areas of ulceration or scarring were seen. The entire gastro-intestinal tract showed a marked hyperplasia of the solitary lymph nodes to the extent of the production of almost pedunculated tumor masses in some parts of the lower ileum. Here and there in the small intestine, injected areas suggesting recent petechial hemorrhage were present. In the cecum this hyperplasia involved almost the entire mucous membrane. The appendix measured 7 cm. in length and 0.5 cm. in diameter. The lumen was greatly narrowed particularly in the distal portion where the wall was thick, boggy, edematous and sclerosed.

### MICROSCOPIC EXAMINATION

*Lungs:* Sections of the left lung showed areas of relative atelectasis; there was no acute bronchitis, pneumonia nor leukemic infiltration.

Sections of the right lung were similar to those of the left, except that there were numerous small areas of subpleural hemorrhage; there was no leukemic infiltration.

*Heart:* There was considerable fat infiltration in the right myocardium and fairly large areas of hyaline degeneration in the left papillary muscle; otherwise, there was no significant abnormality.

*Liver:* There was no thickening of the capsule nor increased fibrous tissue, but many lobules contained considerable fat infiltration. Throughout, there was a diffuse infiltration in the periportal spaces and, to a lesser extent, in the lobules, by large relatively undifferentiated cells of variable size and character. In some areas, the accumulation of these cells was such as to form nodules which were from a few millimeters to a centimeter or more in diameter. The sinusoids were injected and contained many of these cells. The infiltration was of a leukemic type.

Section of the gallbladder showed no leukemic infiltration.

*Pancreas:* There was no leukemic infiltration.

*Spleen:* There was neither thickening of the capsule nor increased fibrous tissue. The lymphoid follicles were greatly diminished. There was marked hyperplasia of the splenic pulp and numerous mitotic figures were present. The sinuses and pulp tissue of the spleen were made up largely of cells of variable size and character,

apparently of myeloid origin, as indicated by the presence of large numbers of eosinophilic leukocytes and myelocytes, and myelocytes of neutrophilic and basophilic type. The predominant cell, however, was of the myeloblastic type in various stages of differentiation. There were numerous megalokaryocytes.

*Kidneys:* There was considerable diffuse leukemic infiltration in the cortex and medulla of both kidneys. In some areas, there was well marked arteriolar sclerosis, but the majority of blood vessels and glomeruli showed no significant sclerosis. There was cloudy swelling of the renal epithelium.

*Genital organs:* Sections of the uterus showed slight chronic cervicitis, multiple fibromyomata and atrophy of the endometrium. There was no leukemic infiltration.

Sections of the ovaries showed a few small peritoneal inclusion cysts and, in one ovary, there were small collections of myeloid cells diffusely distributed in the stroma.

*Adrenals:* A few areas of myeloid infiltration in the medulla and cortex of each adrenal were present.

*Thyroid:* Section of the thyroid gland revealed a colloid goiter, with irregular lobulation and increased stroma; there was no lymphoid or myeloid infiltration. A large amount of colloid material was present and early adenomatous change was observed in some of the lobules. There was an encapsulated adenoma with extensive recent hemorrhage but there was no leukemic infiltration.

*Gastro-intestinal tract:* Section of the stomach showed no abnormality of significance.

Section of the small intestine showed small and localized areas of myeloid hyperplasia in the mucosa.

*Lymph nodes:* Peri-aortic and mesenteric lymph nodes showed marked diffuse hyperplasia of cells similar to those in the spleen, with numerous mitotic figures and, in sections stained with eosin, methylene-blue, Wright's and Giemsa's stain, numerous eosinophilic leukocytes and myelocytes were seen. The predominant cell, however, was of the myeloblastic type.

*Bone marrow:* Sections from the tibia showed normal fatty bone marrow, with no myeloid hyperplasia.

Sections from the spinal bone marrow showed diffuse myeloid hyperplasia, with numerous mitotic figures and large numbers of myeloblastic cells.

The pathologic diagnoses were as follows:

1. Acute myeloblastic leukemia with myeloid hyperplasia of the

# ACUTE MYELOBLASTIC LEUKEMIA

spleen, lymph nodes, liver and intestine and myeloid infiltration of the kidneys, adrenals and ovary.

2. Petechial hemorrhages of the lungs, kidneys and intestines, and ecchymosis of the skin on the groin.
3. Multiple fibromyomata of the uterus.
4. Colloid goiter, with multiple adenomata.
5. Right pleural adhesions and an old infarct of the right kidney.

## CLINICAL DISCUSSION

*C. L. Hartsock:* This case is interesting because all the symptoms seem to have appeared since the time of the accident when the patient fell on her back. It was the consensus of opinion among the physicians here that some internal injury associated with a ruptured viscus and hemorrhage had occurred as the result of the trauma, and it remained to be discovered which organ had been injured and what treatment should be instituted. Immediate operation seemed to be indicated and consultation with the surgeons confirmed this opinion, but this was delayed while further blood studies were made. A differential blood count was made to determine whether the blood clot had become infected and this gave the clue to the correct diagnosis.

An interesting speculation in this case is what would have happened if the patient had been seen one week earlier. The extremely rapid progress of the leukemic condition suggests that no finding of diagnostic significance would have been discovered in the blood one week previous to our examination and the patient undoubtedly would have been subjected to a useless operation.

TABLE I

## Blood Findings in a Case of Acute Myeloblastic Leukemia

Day after admission to Hospital	1	3	4	5	6	7	8
Red Blood Cells	4,890,000			3,920,000		3,610,000	
Hemoglobin	87.0%			71.0%		68.0%	
White Blood Cells	17,600	16,000	15,100	14,700	26,000	36,000	48,000
Neutrophiles	32.0%	14.0%					
Eosinophiles	4.0%	3.0%					
Lymphocytes	7.0%	7.0%					
Myeloblasts	57.0%	75.0%					
Myelocytes	0	1.0%					
Color Index	0.88			0.91		0.94	
Icteric Index	40.0						
Blood Urea	33.0		78.0			105.0	
Creatinine			1.9		2.8	2.7	
Cholesterol						300.0	
Chlorides						478.0	

## PRIMARY THROMBOPHLEBITIS OF THE LEFT SUBCLAVIAN VEIN\*

C. R. K. JOHNSTON, M.D.

Only one case of primary thrombophlebitis of the subclavian vein has been found in the records of the Cleveland Clinic.

The patient, an athletic school-boy aged 18 years, sought medical advice because of pain in the left chest. He had been well until about seven weeks before the examination, when, during a game of basketball, he had begun to notice weakness, numbness and blueness of the left hand and arm which extended up to the shoulder. This condition progressed until the entire left upper extremity was swollen and blue, and the veins of the arm, shoulder and upper left portion of the chest "stood out like cords." Examination by the family physician revealed that the blood pressure in the left arm was 30 mm. lower than that in the right arm. During the following two weeks all these symptoms had gradually subsided.

One week before his admission to the Clinic, or six weeks following the onset of the illness, the patient began to experience dull pain in the region of the left chest just below the nipple line. This pain was increased by deep breathing and was so severe at times that codeine was required for relief. The patient lost no weight, and he did not complain of cough, night sweats, fever or other symptoms referable to systemic disease.

The patient was a tall, asthenic youth whose weight was slightly below normal. His temperature was 98.6° F. and his pulse rate was 75. Except for the presence of some palpable anterior cervical glands, and a slightly enlarged thyroid, examination of the head and neck revealed no abnormalities. The apex of the left chest was flattened and there was diminished expansion and some impairment of the percussion note. The left diaphragm showed diminished descent. A friction rub was heard at the base of the left lung in the anterior axillary line, but there was no evidence of the presence of moisture. The heart sounds were within normal limits, and were of good quality without evident murmurs. While the pulse was the same in each arm, the blood pressure was 128 systolic, 78 diastolic in the right arm, and 114 systolic, 74 diastolic in the left. Distention of the veins of the left arm and shoulder and the upper portion of the chest was caused by lifting a chair with that arm. This distension subsided one minute after cessation of the exertion. The arm did not become cyanosed nor could a thrombosed vein be palpated. Pressure in the left upper quadrant of the abdomen aggravated the pain in the chest.

\* Case report presented at Staff Meeting on October 31, 1934.

## THROMBOPHLEBITIS

A roentgenogram of the chest and mediastinum revealed the presence of no abnormality. Urinalysis, blood count, blood sugar and Wassermann and Kahn tests of the blood revealed no significant deviations from the normal. The sedimentation rate was 78 mm. in one hour.

The diagnosis was thrombophlebitis of the left subclavian vein with secondary pulmonary embolism and fibrinous pleurisy. The treatment prescribed was rest until the fever had subsided, and abstinence from participation in athletics for a period of from six to eight weeks. A recent communication from the patient's mother, eight months subsequent to his visit here, states that the patient has enjoyed good health except for a brief attack of pleurisy which occurred during the preceding month. This may have been caused by a secondary embolus.

The unusual features of the case were that the lesion was on the left, instead of on the right side, as in other cases reported in the literature, and that the rare complication of pulmonary embolism was present.

### DISCUSSION

Primary thrombosis or thrombophlebitis of the subclavian vein is a relatively rare condition, as may be judged from the small number of cases reported in the literature. The analogous condition in the axillary vein is possibly more common and undoubtedly in some cases, the thrombus occludes both veins. In 1920, Cadenat<sup>1</sup> was able to collect only twenty-seven reported cases of primary thrombosis of the axillary vein, while in 1931, Horton<sup>2</sup> stated that more than fifty cases had been reported in the literature up to that time. Reference to the Quarterly Cumulative Index Medicus for the past few years, impresses one with the fact that the incidence of primary thrombosis in the subclavian vein is less than half as great as that of thrombosis in the axillary vein.

Several terms which are used to describe this condition are primary thrombosis, idiopathic thrombosis and effort thrombosis. Irrespective of the terminology, this diagnosis should be made only in those cases in which there is no other obvious cause for the symptoms, such as the presence of malignant or tuberculous glands.

The etiology of this condition has excited considerable interest, and several theories have been advanced, notably those of Lowenstein,<sup>3</sup> and of Gould and Patey.<sup>4</sup> Trauma and strain usually cannot be excluded as etiologic factors, although there may be no direct evidence of injury of the vein. All theories ascribe the phenomena to venous dilation and stasis which are caused by the effort of expiration combined with injury of the wall of the blood vessel.

This injury is usually caused by pressure from some structure, such as the subclavius muscle, costo-coracoid ligament or the first rib, on the intima of the blood vessel. In nearly all cases, the arm is in the abducted position when the supposed trauma is produced.

Thrombophlebitis of the subclavian vein, although a rare condition presents certain definite characteristic findings. Usually the patient is a healthy male between twenty and thirty years of age who presents himself for examination because of symptoms referable to the right arm.\* Almost always there is a history of recent trauma or exceptional effort, while the arm was in the abducted position. The affected arm is uniformly swollen, cyanosed and the superficial veins of the pectoral region and anterolateral chest wall are dilated. In the presence of axillary thrombosis, a firm tender cord is palpable in the region of the vein while in the presence of subclavian thrombosis, no such cord is felt. Usually some pain and tenderness are present, but there is no striking pyrexia or constitutional disturbance. In making a differential diagnosis the following conditions must be considered: intrathoracic tumor, cervical rib or other bony abnormality, enlarged axillary lymph nodes, aneurysm of the arch of the aorta, and, in some instances, cardiac failure. The presence of syphilis and tuberculosis must always be excluded.

The treatment of primary thrombophlebitis is simple and consists of rest followed by massage. The value of ambulatory treatment has been emphasized. The prognosis is uniformly good, although recurrences have been reported.<sup>5</sup> Embolism is a rare complication<sup>6</sup> although it must always be considered as a theoretical danger.

#### REFERENCES

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\* In the case reported here, the thrombus was on the left. Whether or not the patient was left-handed was not ascertained by the examining physician.



## OBSERVATIONS ON THE PHYSIOLOGY OF CORONARY CIRCULATION\*

C. J. WIGGERS, M.D.

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Formerly it was believed that the coronary arteries were end arteries in the true sense. Within relatively recent years, however, and largely as the result of the investigations of Dr. Wearn, this conception has been discarded. Dr. Wearn and his associates have demonstrated that blood entering the coronary arteries has several possible exits. In the first place, of course, it may pass by way of the capillaries and veins into the coronary sinus and then into the right auricle of the heart. Through the capillaries, also, blood may pass into the thebesian veins which communicate directly with the heart chambers. In addition there are vessels of an order larger than capillaries, which pass from the coronary arteries to the lumen of the ventricle or from the coronary arteries to sinusoids situated between the muscle bundles. Lastly, there are rather extensive anastomosing vessels, which arise from the coronary arteries and extend into the pericardium, mediastinum and diaphragm. The extent to which the various pathways, other than those communicating with the coronary sinus, participate in the nourishment of the normal heart is still a matter for conjecture. There is clinical evidence, however, that in the presence of gradual narrowing and occlusion of a coronary artery, an efficient collateral circulation may develop by way of the thebesian veins and the vessels described by Wearn.

Numerous technical difficulties are encountered in attempts to measure the flow of coronary blood. Because of the numerous channels by which blood may escape from the coronary arteries and capillaries, it is essential that the amount of blood, which enters the coronary arteries be measured, rather than the amount of blood which returns through the coronary sinus. Opinion has been divided as to whether there is a forward flow of blood through the coronary system only during diastole or whether flow also occurs during systole. Although the final answer to this problem is not yet available, most recent evidence indicates that there is a period of forward flow during systole as well as during diastole.

*Abstracted by A. CARLTON ERNSTENE, M.D.*

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\* Abstracted by Dr. A. C. Ernstene from paper presented at Cleveland Clinic Staff Meeting October 31, 1934.

## GUESTS

## GUESTS

### NORTH CENTRAL BRANCH OF THE AMERICAN UROLOGICAL ASSOCIATION

The North Central Branch of the American Urological Association held its annual meeting in Cleveland on November 8, 9 and 10th. Members of the Staff of the Cleveland Clinic presented the following program on November 10th.

#### PROGRAM

Surgical Management of Vesico-vaginal Fistula.	Dr. William E. Lower
X-ray Therapy in Malignancies of the Genito-Urinary Tract	Dr. U. V. Portmann
Endocrine Disturbances of Urologic Significance	Dr. E. P. McCullagh
Differential Diagnosis of Right Upper Abdominal Pain with Reference to the Right Kidney	Dr. B. H. Nichols

#### INTERMISSION FOR VIEWING OF EXHIBITS

Diagnosis and Medical Treatment of Urinary Calculi.  
Wax Models of Hypertrophy of the Prostate Treated by Transurethral Resection.  
Wax Models of Operative Specimens.  
Roentgenograms of Kidney Tumors.  
Researches Concerning Male Sex Glands.

Neurogenic Bladder Associated with Brain Tumors	Dr. W. J. Gardner
The Importance of the Prostate in Orthopaedics	Dr. Wallace Duncan
Pulsating Tumors of the Sternum. (Metastatic Hypernephroma. Case Report)	Dr. George Crile, Jr.
Urologic Surgery in Patients with Cardiovascular Disease	Dr. A. Carlton Ernstene
Indications, Technic and End-Results of Adrenal Denervation	Dr. George Crile

#### CLEVELAND OPHTHALMOLOGICAL CLUB

The Cleveland Ophthalmological Club held its second annual post-graduate review at the Cleveland Clinic on December 10, 11 and 12. The program which is listed below included lectures and demonstrations covering many subjects of value and interest to the ophthalmologists who attended.

#### PROGRAM

Monday, December 10

Problems and Procedures in Refraction	Dr. Avery Prangen Rochester, Minn.
Muscle Training—Its Value—Methods	Dr. LeGrande Hardy New York, N. Y.
Spectacles	Mr. Harry Davis Cleveland, Ohio

## GUESTS

Glaucoma—Types—Surgery

Dr. Harry Gradle  
Chicago, Ill.

Neurological Ophthalmology

Dr. Ivan Lillie  
Philadelphia, Pa.

Ocular Illusions

Dr. Otto Glasser  
Cleveland, Ohio

Twenty-five Years' Progress in Ophthalmology

Dr. Harry Gradle  
Chicago, Ill.

### Tuesday, December 11

Papilledema or Papillitis

Dr. A. D. Frost  
Columbus, Ohio

Nonsuppurative Keratitis

Dr. John Gipner  
Rochester, N. Y.

The Writing of Medical Papers

Miss Jessie Tucker  
Cleveland, Ohio

Tinted Lenses—Their Value

Dr. M. W. Jacoby  
Cleveland, Ohio

The Interesting Phases of Ocular Pathology

Dr. Georgiana Theobald  
Chicago, Ill.

The Future of Medicine

Dr. George Crile  
Cleveland, Ohio

Ocular Tuberculosis—A Pathological Review

Dr. Fred T. Tooke  
Montreal

### Wednesday, December 12

Ophthalmological Problems

Dr. W. E. Bruner  
Cleveland, Ohio

Intra-ocular Foreign Bodies

Dr. Edward Stieren  
Pittsburgh, Pa.

Fundus Clinic:

Diagnostic Fundus Lesions with Lantern Slides

Dr. A. B. Bruner  
Cleveland, Ohio

Demonstration of Cases

Dr. Paul Moore  
Dr. Paul Motto  
Dr. Benjamin Wolpaw  
Dr. A. B. Bruner  
Cleveland, Ohio

Several of the commercial houses exhibited apparatus of interest to ophthalmologists and there were exhibits also of tinted lenses, spectacles, exophthalmos, roentgenographic examination of the brain and neurologic surgery.

## GUESTS

### GUEST SPEAKERS

On October 22, 1934, Mr. Arthur Abel of London, England, who had come to this country to participate in the Symposium on Cancer at the meeting of the American College of Surgeons in Boston, spoke at the Clinic.

He described his experiences with the Miles technic of performing the combined abdomino-perineal resection for carcinoma of the rectum. He emphasized that the tumor spreads downward to the ischiorectal space and upward along the course of the inferior mesenteric artery. He strongly recommended that the first step of the operation should be the ligation of the vessels before mobilization of the tumor occurs.

He stressed the importance of glucose solutions administered intravenously before operation, of blood transfusions as a routine procedure in all cases, and of continuous administration of sodium chloride solutions for twenty-four hours after the operation.

He also advised section of the presacral nerve in every case and stated that, in his experience, the incidence of bladder symptoms has been greatly decreased as the result of this procedure. Before this measure was adopted patients who had been subjected to this operation usually required an indwelling catheter for a period of from a week to ten days, and this resulted in a high incidence of bladder infection. When the presacral nerves are severed, there is no spasm of the sphincters and not more than one patient in four has had to be catheterized, and then only once or twice. Section of this nerve not only prevents urinary retention, but increases the peripheral flow of blood.

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On December 21, 1934, Dr. Leonard G. Rowntree, Director of the Philadelphia Institute for Medical Research, was the guest of the Clinic at a luncheon and gave a short talk on tests of vital function.

He mentioned various tests, such as the phenolsulphonephthalein and urea clearance tests of the kidney, the bromsulphalein and van den Bergh tests of liver function, and various estimations of endocrine function, such as the chemical determinations of blood sugar, calcium, phosphorus, phosphatase, etc., which have been, in his opinion, of real diagnostic importance. Attention was called to the fact that the tests should be carefully interpreted, and that their significance should be properly evaluated in relation to the clinical findings. In this connection he cited several amusing examples from his experiences in the Air Service during the War in regard to flyers

## GUESTS

who, by their record of achievements, had proved themselves brilliant aviators, and yet could not pass all the tests that the Army Medical Service devised and used as a basis for admission into the air service.

In discussing his own investigations on the original phenolsulphonephthalein test, he called attention to Bright's brilliant work on kidney disease, and to the importance of the first kidney function test which Bright devised with the use of such humble implements as a candle and a spoon. Dr. Rowntree also explained how the determination of phenolsulphonephthalein excretion could be used in the same way as the findings from the urea clearance test by following the curve of excretion of the dye.

He said that there was a great need for accurate tests of the functional capacity of the liver and discussed the difficulties of trying to measure the function of this complex organ.

In conclusion, Dr. Rowntree stated that the possibilities for research and progress in this field of testing vital functions were enormous, and that up to this time the surface had barely been scratched. He predicted that new methods of approach to endocrine and other physiologic processes would be discovered, and that the future developments in this field would overshadow in scope and importance what already has been accomplished.

## RECENT PUBLICATIONS BY MEMBERS OF THE STAFF AND FELLOWS

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- \*A. Carlton Ernestine and Bert E. Mulvey: A Study of Auricular Fibrillation Following Operations for Goiter, *Am. J. Med. Sc.*, 188:382-386, (September) 1934.
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- Russell L. Haden: The Classification of Chronic Arthritis, *Physiotherapy Review*, 14:142-143, (September-October) 1934.
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- D. R. McCullagh: A New Method for the Determination of Iodine, *J. Biol. Chem.*, 107:35-44, (October) 1934.
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- W. V. Mullin: The Present Status of Infection of the Upper Respiratory Tract in its Relation to Focal Infection, *New England J. M.*, 212:50-52, (January 10) 1935.
- B. H. Nichols and E. L. Shiflett: Osteopoikilosis: Report of an Unusual Case, *Am. J. Roentgenol. & Rad. Therapy*, 32:52-63, (July) 1934.
- B. H. Nichols and E. L. Shiflett: A Supernumerary Rib Arising from the Second lumbar Vertebra, *Am. J. Roentgenol. & Rad. Therapy*, 32:196-197, (August) 1934.
- B. H. Nichols and E. L. Shiflett: Renal Rickets, *Radiology*, 23:677-681, (December) 1934.
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ABSTRACTS OF RECENT PUBLICATIONS  
A STUDY OF AURICULAR FIBRILLATION FOLLOWING  
OPERATIONS FOR GOITER:

A. CARLTON ERNSTENE, M.D. and BERT E. MULVEY, M.D.

Am. J. Med. Sciences, 188:382-387, September 1934.

Auricular fibrillation is the most common cardiac irregularity observed in the presence of hyperthyroidism, and in a considerable number of cases the arrhythmia first appears shortly after thyroidectomy has been performed. This investigation is based on 405 consecutive cases in which thyroidectomy was performed. Adenomatous goiter without clinical or laboratory evidence of hyperthyroidism was present in 192 cases, while in the remaining 213 cases hyperplastic or adenomatous goiter associated with hyperthyroidism was present. Auricular fibrillation was present before operation in 16 patients (7 per cent) who had hyperthyroidism. Postoperative auricular fibrillation developed in 31 (16 per cent) of the 197 patients who had normal rhythm before operation. The arrhythmia also was present before operation in two patients who had adenomatous goiter without hyperthyroidism.

The age of the patient, the type of goiter and the duration of hyperthyroidism appear to be the most important factors predisposing to the development of postoperative auricular fibrillation. The degree of elevation of the basal metabolic rate is of little significance. All the patients in this series were between the ages of thirty-five and sixty-one years, but only five were less than forty years of age. Nine patients had had symptoms of hyperthyroidism for more than thirty months; and in one instance a thyroidectomy had been performed for hyperthyroidism eight years before admission here, and there had been a gradual recurrence of symptoms after four years. Of 35 patients in whom enlargement of the thyroid was present, the symptoms had existed from one to more than forty years in the 27 patients who were able to estimate its duration. Noticeable goiter had been present for less than five years in three of these 27 cases.

The results of this study indicate that the factors which predispose to the development of postoperative auricular fibrillation are the same as those which govern the occurrence of arrhythmia in the presence of hyperthyroidism before operation is performed. In postoperative auricular fibrillation, however, an additional stimulus connected with the operation or the early postoperative course is necessary to initiate the arrhythmia. The immediate increase in the rate of metabolism following operation probably is the essential factor responsible for the initiation of the arrhythmia.

## ABSTRACTS

Postoperative auricular fibrillation is more common both relatively and absolutely in patients with adenomatous goiter than in those with hyperplastic goiter. This fact cannot be accounted for entirely by differences in the ages of the patients belonging to the two groups. The long duration of thyroid enlargement in the majority of cases of adenomatous goiter suggests an explanation for the more common occurrence of postoperative fibrillation in this group. It is possible that many of these patients have experienced repeated or prolonged periods of low-grade, unrecognized hyperthyroidism, before symptoms appeared which were of sufficient severity to necessitate medical advice. Such subclinical thyrotoxicosis might favor the gradual progression of myocardial damage and thus predispose to the development of postoperative auricular fibrillation.

Postoperative auricular fibrillation generally begins during the first sixty hours after operation. It rarely causes circulatory embarrassment, and normal rhythm usually is re-established spontaneously within forty-eight hours after its onset. However, gradual digitalization is begun with the onset of the arrhythmia, so that the complete effect of the drug can be obtained more readily in the rare instances in which mild congestive failure does develop. If the arrhythmia should persist for more than a week, quinidine may be used to restore normal rhythm.

BENIGN STRICTURE OF THE INTESTINE DUE TO IRRADIATION OF  
CARCINOMA OF THE CERVIX UTERI:

E. N. COLLINS, M.D. and THOMAS E. JONES, M.D.

Surg. Gynec. Obst., 59:644-649, (October) 1934.

Four hundred and twenty-two patients with carcinoma of the cervix have received irradiation at the Cleveland Clinic. This total number includes six cases (1.4 per cent) of benign stricture of the intestine which might easily have been confused with metastatic carcinoma. Subsequent to the irradiation no evidence of carcinoma was found, and, judging by present standards, none of these patients received excessive irradiation. It seems probable that the incidence of this lesion is found to be greater elsewhere as well as in this institution than the literature would indicate.

The present study directs attention to this benign lesion as a clinical entity, and offers suggestions for its prevention. It appears logical that this complication may be prevented without altering the principles of the well-proved, present efficacious radiation therapy of cervical cancer. Although there are many reports in the literature which deal with the manifestations of acute injury of the intestine following irradiation, no reports were found wherein the patients recovered from the acute symptoms and at a later time symptoms developed which were referable to benign stricture of the intestine. This condition may represent a later stage of the inflammatory process than has hitherto been observed. Of the six cases reported, five of the benign strictures occurred in the sigmoid colon and one in a loop of the lower part of the small intestine.

A patient who complains of unusual abdominal symptoms, particularly if they simulate those of intestinal obstruction, several months or even years following radiation therapy, may have a stricture of the intestine due to irradiation, and such a patient may be restored to normal health by a resection of the lesion. Before the disability is attributed to metastasis, a re-examination should eliminate the possibility of the presence of this curable condition. At least roentgen examinations of the sigmoid and colon should be made, and a careful roentgen study of the small intestine may be advisable, provided the obstruction is not complete. It is advisable to explore the abdomen, particularly in cases in which there is evidence of intestinal obstruction, and in which there is no evidence of the presence of carcinoma remaining in the pelvis.

The lesion may show any stage of chronic inflammation at the time of examination, but an annular fibrosis which results in a narrowed lumen was the predominant finding in the cases observed. If ulceration is present, it may involve only the mucosa, or it may

extend through all the layers of the intestine into the adjacent mesenteric fat. No evidence of acute perforation into the peritoneal cavity was found in this series of cases.

In making a diagnosis of the lesion, the history relative to bowel function is of first importance, and minute inquiry should be made concerning the condition of the patient immediately following operation. When a stricture caused by irradiation is forming, although diarrhea is often the predominant symptom, unusual constipation supervenes sooner or later, which is accompanied by other symptoms of varying degrees of intestinal obstruction. If the patient is seen during the ulcerating stage of the disease, intestinal hemorrhage may be the chief complaint.

In the cases in which lesions of the sigmoid were present, the sigmoidoscopic examination did not reveal the lesion, because of the unusual fixation of the involved area, or because of an unusually redundant sigmoid colon which was distal to the lesion. The roentgen examination of the colon was the most important single means of revealing the presence of the lesion in the sigmoid colon. Modifications of the usual roentgen procedures were used.

The dosage of radium administered to these patients varied from 2,440 millicurie hours to the equivalent of 4,240 millicurie hours. One patient received only radium irradiation. Tubes of radon containing 1.5 mm. of brass filter enclosed in 2 mm. of rubber were used in all cases. In addition, in one case, radium needles were inserted into the carcinomatous tissue. Roentgen therapy was administered through four portals—the suprapubic, the right iliopubic, the left iliopubic and the postsacral regions, each portal in succession receiving 50 per cent of a skin unit dose at a time, and the entire course of treatment in each instance being given in from five to seven days. The skin unit dose was 800 roentgens and the estimated 10 cm. depth dose was 30 to 40 per cent, a potential of 200 kilovolts being used, 5 to 8 milliamperes with filtration varying from 0.5 to 1.0 mm. copper and 1 mm. of aluminum and varying sized portals at 50 cm. focal skin distance, depending on the thickness of the abdominal wall. The total calculated roentgen dose about the cervix was approximately 800 roentgens.

In considering the etiology of the lesion it is pointed out that if a segment of intestine is to be affected by the radium irradiation, it must lie very close to the treated area, and must remain more or less constantly in that position during the time the radium is in place. The factors used in the roentgen therapy produce a homogeneous irradiation to the entire contents of the pelvis. No one segment of intestine should receive more roentgen irradiation than any other

## BENIGN STRICTURE OF THE INTESTINE

segment. If it is kept in mind that only one of these patients received only radium therapy, it is logical to assume that in the patients who received both types of irradiation, roentgen therapy aggravated a condition already started by the radium therapy.

Certain measures which are suggested for the prevention of benign stricture of the intestine following irradiation are the following:

1. If the patient is placed in a moderate Trendelenburg position during the time of the radium irradiation, the danger of dislodgement of the radium is minimized, and the lesion may be prevented unless the vulnerable, redundant segment of intestine is fixed in position at the time of the irradiation.

2. Continued peristaltic activity of the intestine during the time of irradiation might also be a means of changing the position of redundant loops of intestine. The administration of pitressin after the usual preparation by a thorough emptying of the intestine is suggested as a means of producing this desired effect.

3. The keeping of the tip of a flexible colon tube in the sigmoid colon during the time of radium application might be helpful in preventing an accumulation of gas, which might predispose to the development of a benign stricture in this area.

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### **In Memoriam**



**DR. WILLIAM V. MULLIN**

**1884-1935**

Dr. William Valentine Mullin, Head of the Department of Otolaryngology of the Cleveland Clinic, died at the Cleveland Clinic Hospital on April 25 from cavernous sinus thrombosis of unknown origin.

Dr. Mullin who was one of the most distinguished otolaryngologists of this country was born in Iowa City, Iowa, on February 14, 1884. He was a student at the University of Iowa from

## IN MEMORIAM

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1902-1904 and secured his medical degree from the University of Denver in 1908. He was in general practice in Holly and Colorado Springs, Colorado, until 1910 when he decided to specialize in otolaryngology. He practiced his specialty at Colorado Springs until 1926 when he became the head of the otolaryngological division of the Cleveland Clinic. In 1914 he took post graduate work in Germany at the Killian and Halle Clinics.

Dr. Mullin was a member and had been an officer of all the leading medical organizations pertaining to his specialty. He was a Fellow of the American Medical Association and of the American College of Surgeons; from 1926-1928 he was secretary and in 1929 chairman of the section on laryngology, rhinology and otology of the American Medical Association; chairman of the section of laryngology of the Cleveland Academy of Medicine and of the Ohio State Medical Society in 1931 and 1933 respectively. In 1926 he was vice-president, in 1933 treasurer, and in 1934 secretary of the American Laryngological Association; he was secretary of post-graduate instruction of the American Academy of Ophthalmology and Oto-Laryngology. In addition to the above societies he was an Examiner of the American Board of Oto-Laryngology and a member of the American Otolological Association, the American Laryngological, Rhinological and Otological Association, the Association for the Study of Allergy, and the American Medical Editors and Authors Association.

During the World War he became a Lieutenant in the Medical Corps of the U. S. Army and was stationed at Oteen, North Carolina in General Hospital No. 19, where he remained throughout the War in spite of repeated efforts to be sent overseas.

In 1913 he married Louie M. Nichols of Colorado Springs, who with a daughter, Harriet C. Mullin, survives him.

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## MEMORIAL ADDRESS \*

William E. Lower, M.D.

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We are gathered this afternoon to pay tribute to the memory of a man whom we shall see no more. Another river of life has run out into the uncharted sea. I realize full well that we cannot drown sorrow nor gild grief with words, but we can temper our emotions by the memory of the good deeds of those whom we loved. Bill Mullin is dead — but only the mortal part has passed to the Great Democracy of Death. The immortal — the fine deeds, the kindly acts, the gracious and loving sympathy will live on always.

Others will speak of his pre-eminence in his specialty, of his good fellowship. But I cannot speak of him as a colleague without touching upon all his qualities because upon those very qualities rested his value to those of us who had the privilege of working with him.

There was no department in the Clinic in which he was not interested. He criticized sharply sometimes, but always constructively. He was not always angelic but always emphatic. Every one knew where he stood. He had independence and courage. His promise was a fulfillment. His enthusiasm for his work and for the success of the Clinic was unbounded. His influence on all the personnel of the Clinic was masterful; it was wholesome, stimulating and well worth emulating. His characteristics are a heritage which "it seems to me one well might wish to hold in fee."

He was a man of strong convictions. He fought hard for things in which he believed, but if shown a better way, he submitted and supported. His interest was never lukewarm, it was always hot.

He loved friends, and had hosts of them, but his close friends he cherished as something sacred. He was a great companion. He loved the mountain and the forest and the stream, and revelled in Nature's colorings. I shall miss him in the Spring rides along the trails when Nature is budding forth. He always admonished me to let him know when the trillium and dogwood were in full bloom, and I never failed to do so for his presence added to the full enjoyment and pleasure of the ride. In the golden Autumn we sought the hillside with the richest coloring. He was a real

\*Address delivered at Memorial Service for Dr. William V. Mullin at the Cleveland Clinic April 27, 1935.

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### MEMORIAL ADDRESS

Nature lover. If he saw anything in passing which interested him he would stop and get all the information possible and then read about it. What he knew he knew well. His interests were wide.

His greatest interest, however, was in his chosen profession. He stood at the very top in his specialty. He was a leader, not a follower. He sought the intellectual light in his work. His face was always toward the East. He was a great diagnostician, a skilled technician. He had a gentle, human touch.

""Tis the human touch in this world that counts,  
The touch of your hand and mine,  
Which means far more to the fainting heart  
Than shelter and bread and wine.  
For shelter is gone when the night is o'er  
And bread lasts only a day;  
But the touch of the hand and the sound of the voice  
Sing on in the soul away."

When a new idea struck him, it hit him hard and like a child with a new toy, he would find a listener and tell him about it. We knew his quick, firm footstep and when I saw him coming on our corridor, I could tell at a glance whether it was a new thought or a new worry which prompted the visit.

Hearts break, men die, flowers bloom, leaves fall — but the world moves on. Bill Mullin would not have us stop a minute because of his passing. We must carry on the lighted torch as we shall. Farewell, dear Colleague, we are richer in wisdom for your having worked with us.

"Life's work well done;  
Life's race well run;  
Life's victory won;  
Now comes rest."  
Hail and farewell.

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## THE TECHNIQUE OF ABDOMINOPERINEAL RESECTION FOR CARCINOMA OF THE RECTUM\*

THOMAS E. JONES, M.D.

The primary object of any operation for cancer of the rectum or rectosigmoid must be the eradication of the disease. The pathologic observation regarding the lymphatic spread which has been so well demonstrated by Miles makes it quite apparent that the combined abdominoperineal operation fulfils this purpose better than any other type of procedure so far devised.

Spinal anesthesia is preferable in performing this operation. Then the patient should be placed in the Trendelenburg position, which makes it easy to pack the intestines well out of the pelvis. This is an essential requirement because the operation necessitates deep pelvic dissection. A midline or left rectus incision is the next step and the liver is explored for metastasis. One nodule does not contraindicate operation. Multiple nodules do. The gland-bearing area is then examined, only, however, to note the extent of malignant invasion. Even extensive involvement of the nodes does not contraindicate operation. Finally the growth is inspected if it lies above the reflection of the pelvic peritoneum. If there are multiple small nodules on the peritoneum, operation is contraindicated unless the area which contains them can be resected widely.

If all these conditions favor going ahead with the operation, the sigmoid is then examined. Occasionally it is necessary to mobilize the sigmoid by cutting its peritoneal attachments on the lateral side (Fig. 1). The location of the inferior mesenteric artery is then determined and this vessel is ligated below the first sigmoid branch (Fig. 2). The Cameron light is very useful for this procedure unless the mesocolon is too thick. In the latter case the artery is exposed by incising the peritoneum of the mesentery about an inch below the bifurcation of the aorta. Ligation of this vessel insures a bloodless field for the pelvic dissection.

The succeeding step is incision of the peritoneum on each side of the mesosigmoid down to the promontory of the sacrum. These lateral incisions are continued down until they meet anteriorly behind the base of the bladder in the male or the pouch of Douglas in the female. (Figs. 3A, B, C.)

Traction on the bowel then brings into view the areolar space between the anterior surface of the sacrum and the mesocolon.

\*Reprinted by permission from the American Journal of Surgery, 27:194-200, February, 1935.

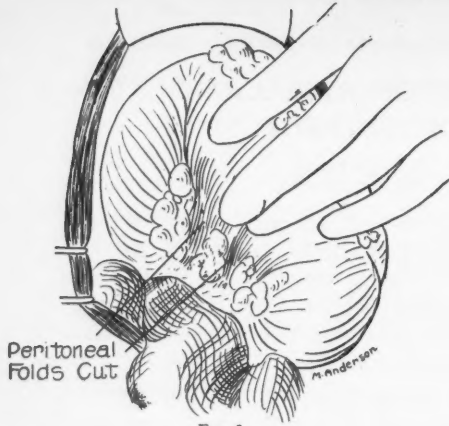


FIG. 1

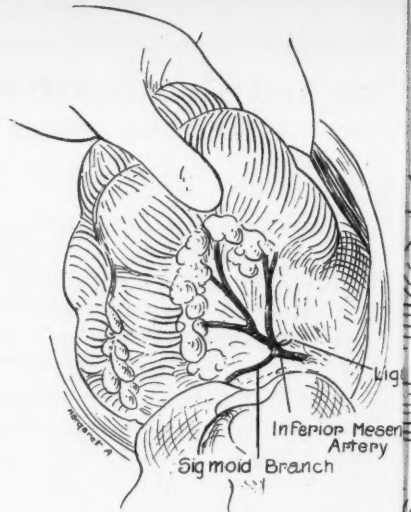


FIG. 2

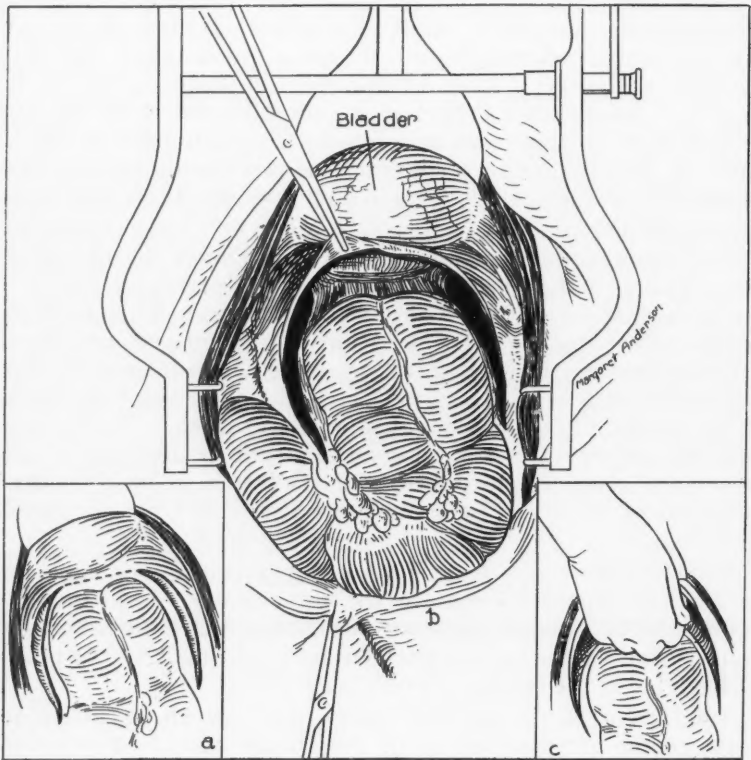


FIG. 3



## THE TECHNIQUE OF ABDOMINOPERINEAL RESECTION

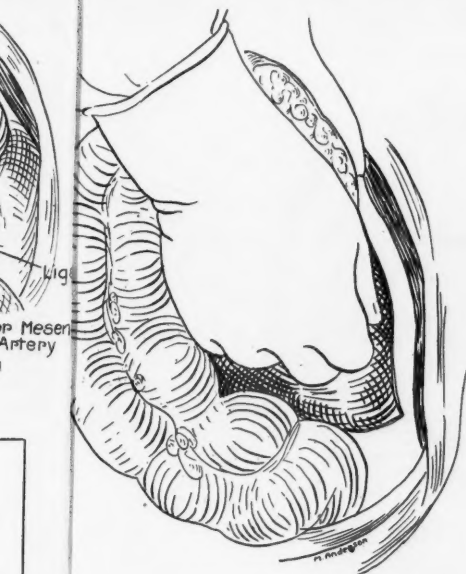


FIG. 4

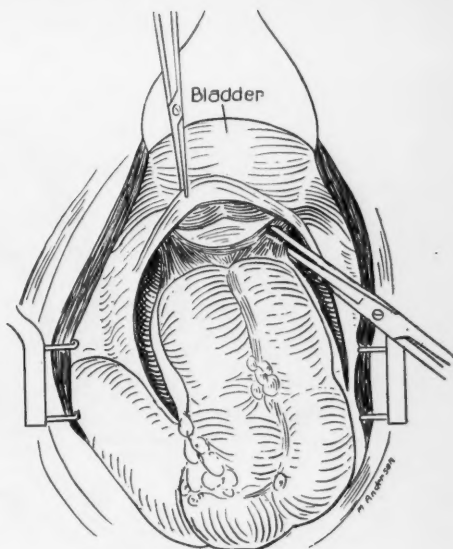


FIG. 5

The fingers and eventually the hand are placed into this space and the pelvic colon and rectum can be easily stripped and pushed forward as far as the sacrococcygeal joint (Fig. 4).

The next step consists in the dissection of the anterior wall from its attachments. The peritoneum at the base of the bladder has been incised and this brings into view the seminal vesicles. These are pushed forward until the upper border of the prostate is felt. This procedure can be carried out with the fingers or under direct view with heavy blunt dissecting scissors. The cut edge of the peritoneum at the base of the bladder is now picked up and the four fingers are placed between it and the bladder. This portion of the peritoneum is pulled up gently until a good-sized flap is obtained which is to be utilized in the reconstruction of the pelvic floor (Fig. 3c). Traction on the bowel renders prominent the lateral attachments of the rectum which are divided (Fig. 5).

This completes the pelvic dissection and the colon is divided between clamps with the cautery (Fig. 6A). Both ends are tied with a heavy silk suture and a piece of rubber tissue is fastened over each end (Figs. 6B, C). This can be accomplished much more quickly than inversion of the ends and carries with it much less danger of contamination of the operative field. The Miles three-blade clamp may also be used for this procedure.

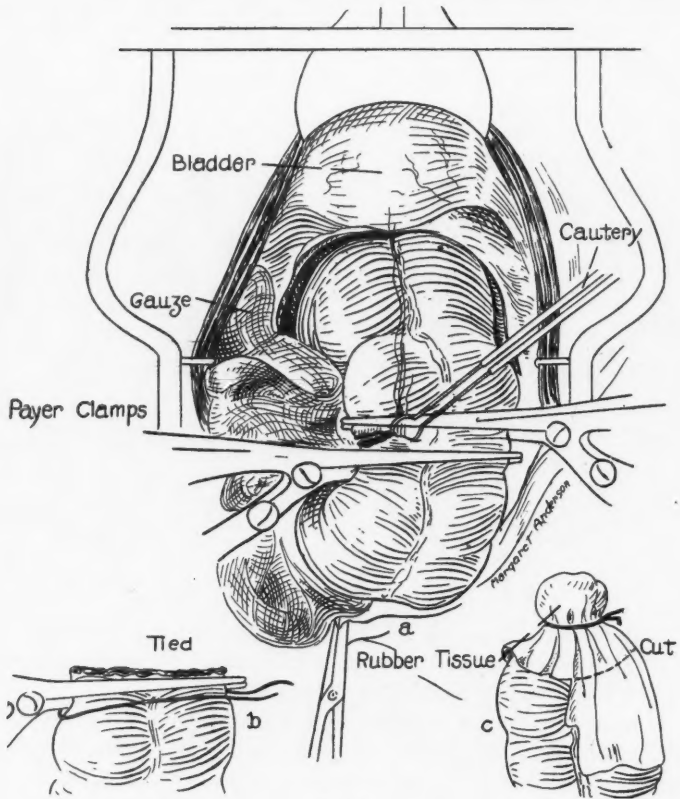


FIG. 6

The end of the distal part of the pelvic colon is then pushed downward into the presacral space where it is easily accessible when the perineal part of the operation is being performed.

The next step consists of reconstruction of the pelvic floor from flaps of peritoneum from the base of the bladder and the lateral pelvic wall (Figs. 7A, B). Under no circumstances must any tension whatsoever be applied in this procedure. In cases in which these flaps cannot be brought together without undue tension, a graft of omentum is used to fill in the defect. Under no condition should the omentum be sewed around the flaps of peritoneum, for this predisposes to obstruction. The uterus and broad ligaments can be utilized in the female in the reconstruction of the new pelvic floor.

## THE TECHNIQUE OF ABDOMINOPERINEAL RESECTION

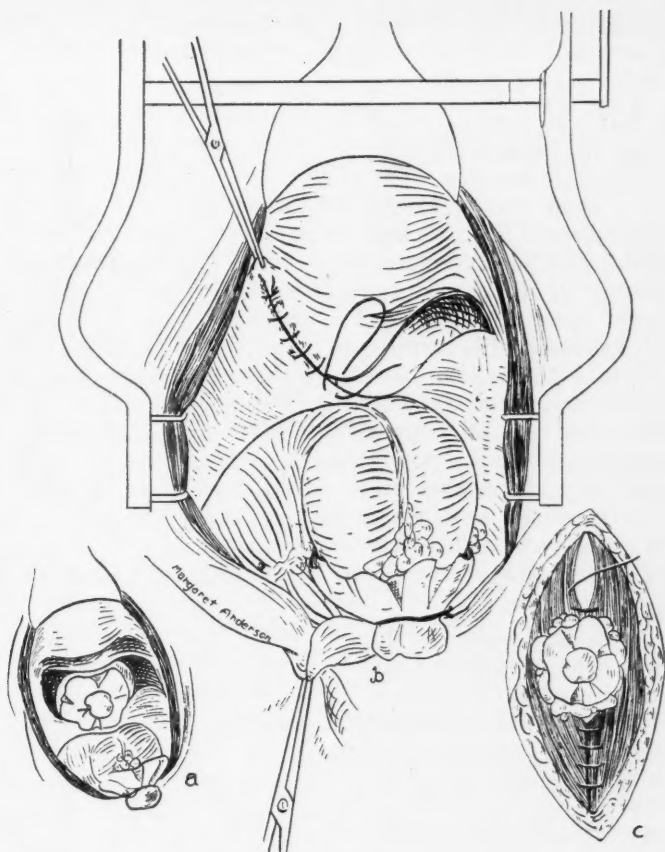


FIG. 7

The proximal end of the colon is then brought out for the construction of the permanent colostomy (Fig. 7c). If the loop is long, it is preferable to bring it out through the original abdominal incision (Fig. 8). With proper protection of the wound, infection is not to be feared. The opening in this position is more satisfactory to patients, because regardless of whether they wear a colostomy bag or other dressings, the abdomen looks symmetrical, which is not the case with an inguinal colostomy. If the sigmoid loop is short, it is brought out through a left McBurney incision.

After closure of the abdomen, the patient is placed in the Kraske position and a purse-string suture is placed about the anus.

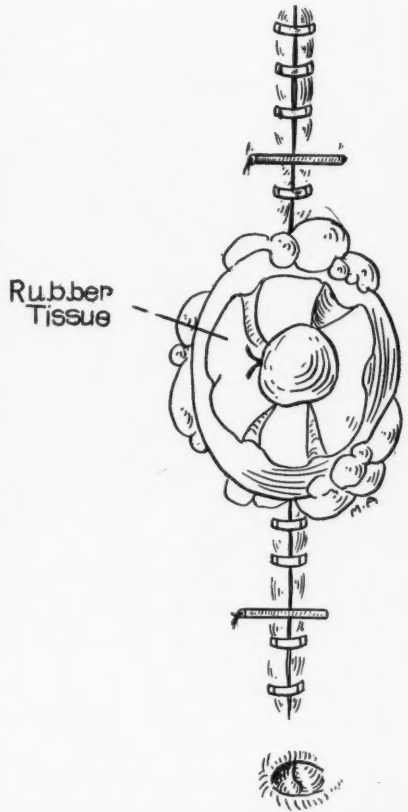
THOMAS E. JONES

A longitudinal incision is made in the midline to within  $1\frac{1}{2}$  inch of the anus and then encircling the anus to include a wide area (Fig. 9A).

The flaps on each side are then dissected back to the edge of the gluteal muscles. The coccyx is then disarticulated from the sacrum (Fig. 10) and the fascia immediately beneath it is incised. If the abdominal part of the operation has been properly executed, this permits entrance into the cavity containing the pelvic colon. The sacrococcygeal muscles are then cut on each side and the bowel is drawn out and stretched until the levator anus muscles are brought into view. These are divided as far away from the rectum as possible.

The anterior wall of the rectum is then separated from the prostate and the dissection is carried down anteriorly until the operation is complete (Fig. 11). A catheter in the bladder is always useful as a guide so that the membranous portion of the urethra may not be injured.

There now remains a large cavity which obviously must heal in by granulation and this requires from eight to twelve weeks. According to Miles' suggestion, a large thin rubber sheet is placed in this cavity into which gauze is packed. By using the rubber sheet, the gauze does not become adherent to the delicate pelvic floor which may tear away (Fig. 12). This method of packing supports the new pelvic floor and also prevents oozing from the large raw surface. Half of the gauze is removed on the third day after operation and the remainder of the packing, including the rubber sheet, on the fourth day.



Umbilicus

FIG. 8

## THE TECHNIQUE OF ABDOMINOPERINEAL RESECTION

The cavity then is irrigated with 1:8000 bichloride of mercury solution, boric acid or permanganate solution.

The colostomy is opened on the second or third day depending upon the amount of abdominal distention. Liquids are allowed from the second postoperative day, if the patient does not complain of nausea.

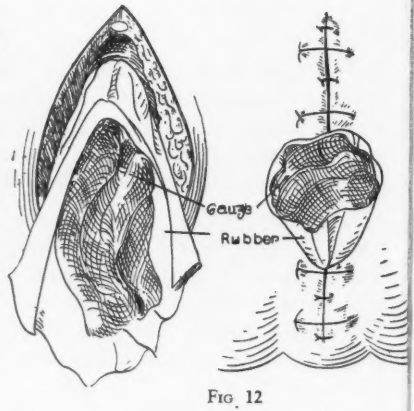
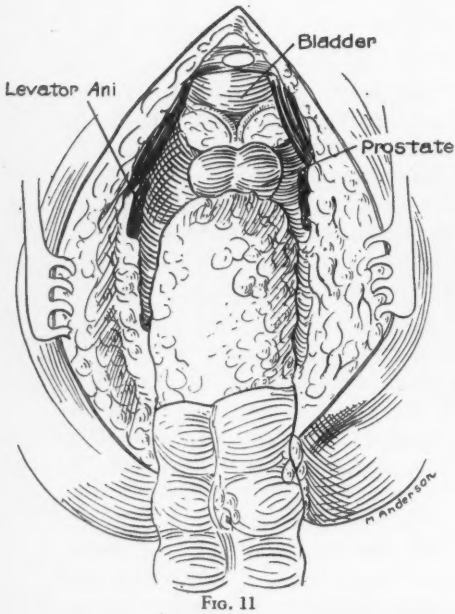
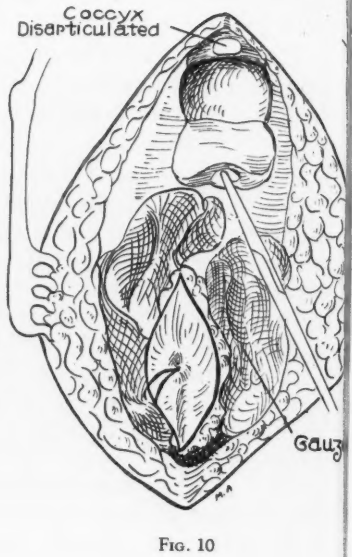
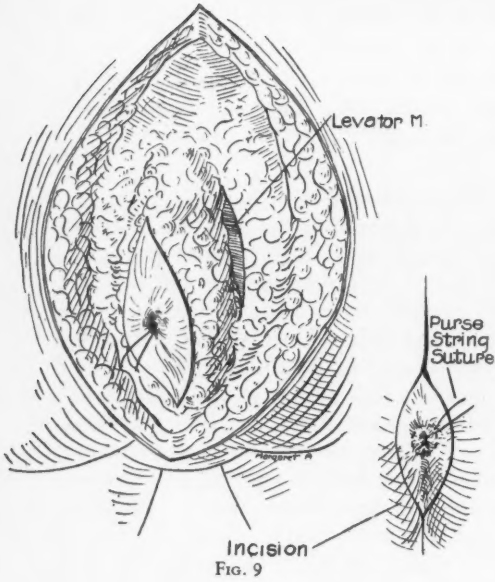
### GENERAL CONSIDERATIONS

The success of the operation is dependent on several factors. First among these and of the utmost importance is the preoperative care. In a majority of these cases, chronic intestinal obstruction has existed for weeks or months and the contents of the colon are infected, but if enough time is allowed and a careful regimen is instituted, the intestines can be decompressed.

The patient is kept in bed, but is allowed to get up to go to the toilet. Saline laxatives have proved most effective. One ounce of magnesium sulphate is placed in 8 ounces of water and the patient takes one ounce of the solution every half hour until it is consumed. This is continued for five, six or seven days. In addition, the patient receives a plain water enema daily. A high calorie non-residue diet is taken and in addition the patient receives 500 or 1000 c.c. of a 10 per cent solution of glucose daily. During his stay in the hospital the kidney function is checked and the blood groupings are determined for transfusion, which is a routine procedure either just before or after operation.

On the day before operation all purgatives and enemas are discontinued and three or four drachms of paregoric are administered during the day. If the hemoglobin has been below 70 per cent, a transfusion is given the patient immediately before operation. During the operation, the ratio of the pulse rate and blood pressure is watched carefully and whenever the indications call for it, 10 minims of adrenalin are given hypodermically. To avoid unnecessary handling, the bed is brought to the operating room.

After operation, the patients, particularly the obese, barrel-chested type, may be placed in an oxygen tent for the first twenty-four hours. No food or liquid is allowed by mouth the first day; after that, water is permitted if there is no nausea. Sodium chloride solution by the subcutaneous route or glucose solutions intravenously are administered daily until sufficient fluid can be taken by mouth. The colostomy may be opened any time, depending on the degree of abdominal distention or the discomfort of the patient. If it has to be done during the first forty-eight hours after operation, a catheter may be placed in the colostomy and the bowel can be tied around it to prevent too much soiling.





## THE TECHNIQUE OF ABDOMINOPERINEAL RESECTION

If the wound has been covered with collodion, there is no appreciable danger of serious infection of the wound. About the tenth postoperative day, any excess bowel outside of the abdomen is cauterized away down to about  $\frac{1}{4}$  to  $\frac{1}{2}$  inch above the skin. This prevents any retraction when healing takes place.

The catheter is left in the bladder for about four days and if the patient is unable to void after that, he is catheterized two or three times a day so that there will be no overdistention. The patient is encouraged to get out of bed on the fourteenth day. Assumption of the upright position allows the new pelvic floor to sag little by little, which aids in the early filling of the posterior cavity. The average stay in the hospital after operation has been twenty-four days.

On account of the necessity for frequent dressings which are required for some weeks, usually some member of the patient's family is taught the proper technique so that it is necessary that a physician see him only once a week. As soon as the colostomy is well healed, the patient is taught to irrigate the colon every two days and if a thorough evacuation is possible, in many cases there is no soiling until the next irrigation is made. Under this condition, only a small dressing is necessary underneath an abdominal binder. Where this can not be so satisfactorily regulated, a colostomy bag is worn.

In a series of 127 cases in my experience there have been 14 deaths, a mortality of 11 per cent. In 52 per cent there has been immunity from recurrence for five years or more; in 63 per cent the patients have been free from cancer from three to five years; and in 70 per cent there has been no demonstrable recurrence under three years.

## UROLOGIC PROBLEMS IN CHILDHOOD \*

WILLIAM J. ENGEL, M.D.

The problems presented by diseases of the urinary tract in children have a right, I think, to be segregated from the other problems with which the urologist is confronted, not only because these diseases in childhood differ in many respects from those in adults, but also because attention is thus directed to lesions in the urinary tract in children which are all too often



FIG. 1.—The patient was a girl, four and one-half years of age, who had had pyuria for three years.

Roentgenogram shows a large calculus in the right kidney.

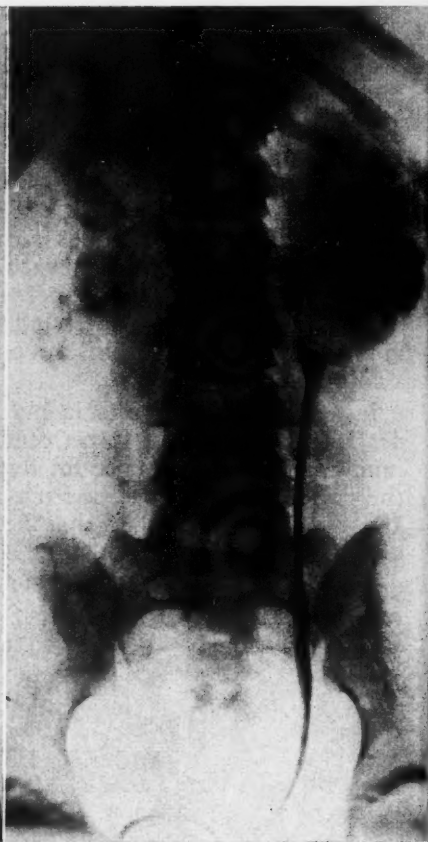
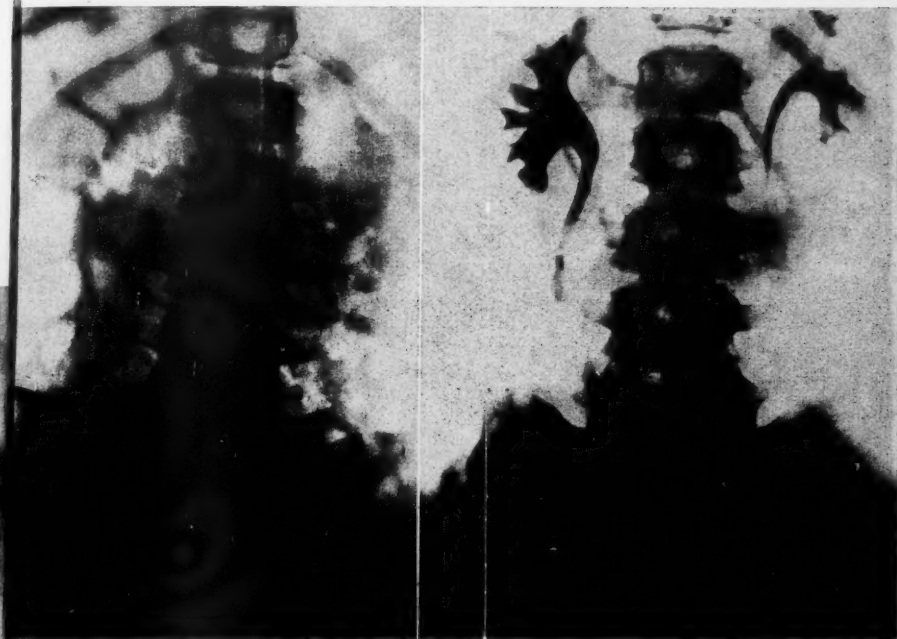


FIG. 2.—The patient was a girl nine years of age.

Roentgenogram shows calculous pyonephrosis of the right kidney and hydronephrosis of the left kidney, an aberrant artery.

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FIGS. 3A and 3B. The patient was a boy twelve years of age. FIG. 3A (*left*) Plain roentgenogram shows a shadow in the region of the right ureter. FIG. 3B (*right*). Intravenous urogram shows the shadow to be a calculus in the ureter. There is hydronephrosis of the right kidney.

overlooked. Many phases of urinary diseases in children might be discussed, but I have chosen to emphasize certain problems relating to the upper urinary tract.

Urologic diagnosis in infants and young children is rendered more difficult because of the impossibility of eliciting subjective symptoms accurately and because physical examination is so often unsatisfactory. The diagnostic methods, however, differ in no way from those employed in adults, and roentgenologic examinations play a major role in all cases. Every child who is suspected of having some disease of the urinary tract should have a

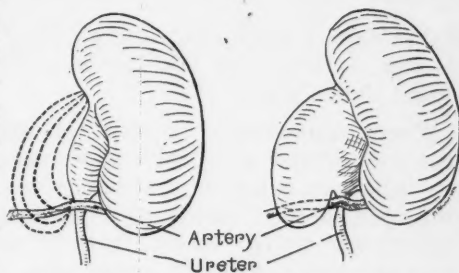


FIG. 4.—Schematic drawing, showing successive stages of dilatation of the kidney pelvis over an aberrant artery.



FIGS. 5A and 5B. The patient was a boy nine years of age. Fig. 5A (*left*). Retrograde pyelogram shows marked hydronephrosis and almost complete destruction of the kidney tissue. Fig. 5B (*right*) Photograph of specimen, showing marked hydronephrosis due to aberrant artery which is well demonstrated.

preliminary stereoroentgenogram of the kidneys, ureters, and bladder, followed by additional studies according to the individual indications.

When intravenous urography was introduced it was hoped that this would solve the problem of urologic diagnosis in children, but it has not completely met these expectations. Although it is employed more or less routinely as a preliminary investigation, it has been, on the whole, rather disappointing as regards final diagnosis and in many instances it has been necessary to resort to cystoscopy and retrograde pyelography before any final decision could be reached. This experience is supported by Campbell's recent report of 304 urograms in children, of which only 47.5 per cent were of diagnostic value and only 7 per cent furnished the

## UROLOGIC PROBLEMS IN CHILDHOOD

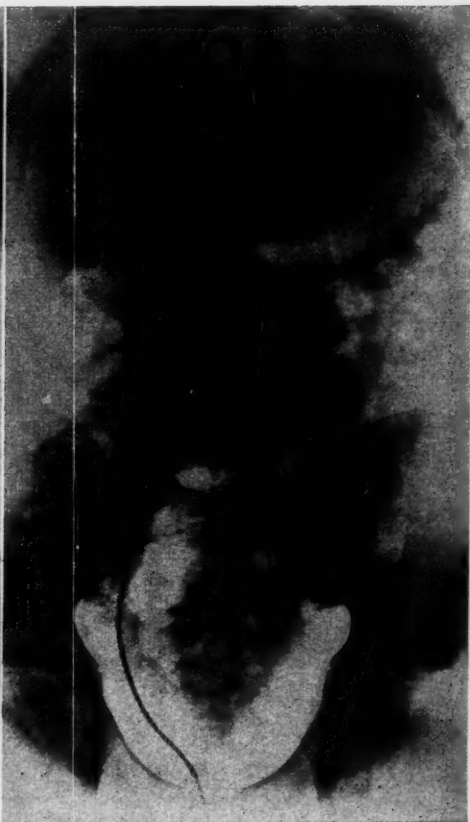
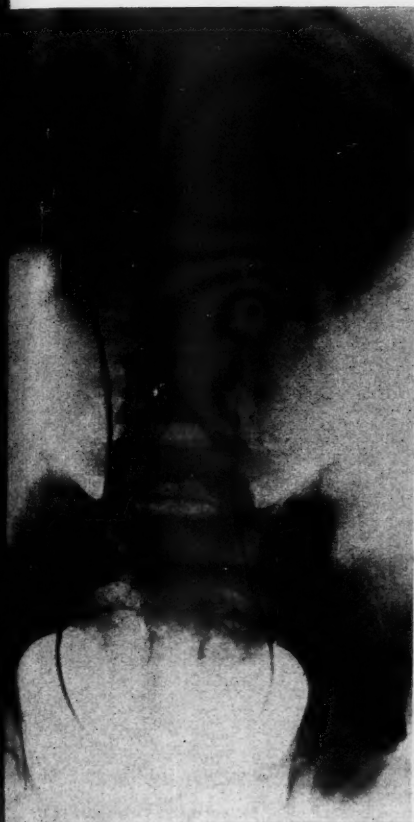
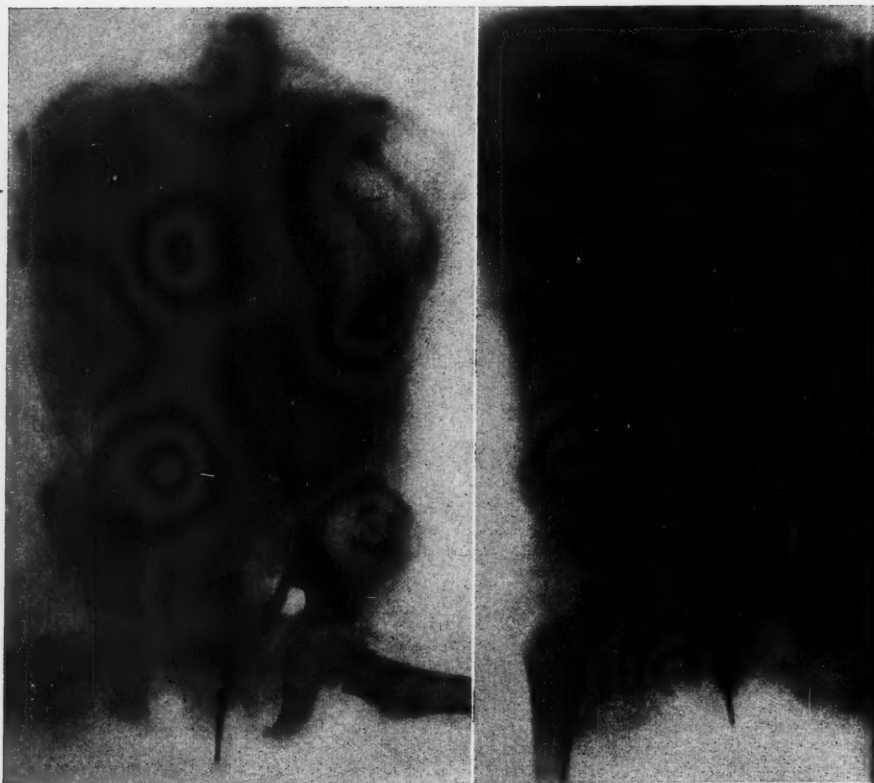


FIG. 6.—The patient was a boy sixteen years of age. Intravenous pyelogram shows bilateral hydronephrosis due to aberrant artery.

FIG. 7.—The patient was a boy fifteen years of age. Retrograde pyelogram shows hydronephrosis due to an aberrant artery. Complete relief of symptoms was experienced after conservative operation.

correct diagnosis without further study. I do not mean to underestimate the value of intravenous urography. It has been of tremendous assistance, but one must be prepared to proceed further in that considerable group of cases in which intravenous urography does not yield conclusive diagnostic evidence. There should be no hesitancy in proceeding to cystoscopy, ureteral catheterization, and retrograde pyelography. Cystoscopy can be safely carried out, no matter how young the patient, and in gentle hands does not increase the hazard.

I shall now discuss some of the specific problems presented by



FIGS. 8A and 8B.—This is a case of congenital megalo-ureter. The patient was a girl, three years of age, who had had chills and fever since she was four and one-half months of age. FIG. 8A (*left*) Right pyelogram. FIG. 8B (*right*). Left pyelogram shows bilateral dilatation of ureters. Bilateral vesicorenal reflux was demonstrated later by cystogram.

the different diseases of the upper urinary tract in children. These may be grouped under three headings: (1) urinary calculi; (2) upper urinary lesions of congenital origin, under which I have included aberrant arteries, congenital megalo-ureter, and ureterovesical stricture, and (3) kidney tumors.

#### URINARY CALCULI

Urinary calculosis is not common in children when compared with the incidence of this condition in adults. In a series of 1,388 cases of urinary calculi seen at the Cleveland Clinic there were 17 cases in children under fifteen years of age, or an incidence of 1.2 per cent. As in the case of adults, stones may occur anywhere along the urinary tract. In our group of cases there were seven in



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the kidney, seven in the bladder, one in the bladder and kidney, two in the ureter only, and one in the kidney, bladder, and ureter.

The clinical picture differs in no way from that seen in the adult. Pain, of course, is the outstanding symptom. In children, however, this is much more frequently associated with rather marked gastro-intestinal symptoms, such as nausea and vomiting, and often muscle spasm of the abdominal wall. This may lead to considerable confusion in diagnosis and an intra-abdominal lesion often is suspected in these cases. The findings of pus cells and red blood cells in the urine, however, should lead one to suspect the true nature of the trouble. Persistent pyuria, especially, should lead to the suspicion of kidney stones. In all cases in which this symptom is present, a plain roentgenogram should be made. This will show stones in the vast majority of instances (Figs. 1, 2, 3A, and 3B).



FIG. 9.—The patient was a boy eight years of age who had had recurrent attacks of chills and fever, associated with pyelitis, since he was six months of age. Retrograde pyelogram shows dilatation of the kidney pelvis and ureter with ureterovesical stricture.

When there is a stone in the bladder the diagnosis is sometimes confused by the presence of urinary incontinence and enuresis. Some neurogenic cause of these symptoms is often wrongly suspected and an erroneous diagnosis of cord lesion or spina bifida may be made. The intense dysuria, however, should always suggest the possibility of stone in the bladder. The diagnosis, of course, is made finally by the finding of stone shadows in the plain roentgenogram of the kidneys, ureters, and bladder. Al-



FIGS. 10A and 10B.—The patient was a boy fourteen years of age. A (*left*) and B (*right*). Bilateral pyelograms, showing marked hydro-ureter and hydronephrosis (*left*). Obstruction in this case was due to congenital bilateral ureterovesical stricture.

though this diagnostic method is available to practically every practising physician, it is amazing to see how often urinary stone goes unrecognized in children.

With improved knowledge of diet and infant feeding the incidence of stone in children has shown a sharp decrease in those countries where it formerly was quite prevalent. The work of McCarrison, Osborn and Mendel, Higgins, and others, showing that urinary calculi develop in a large proportion of rats fed on a diet deficient in vitamin A, forms the basis of this improved dietary management. Much has been accomplished in the way of prevention of stone in children, but there are unquestionably other factors beside diet which enter into the production of uri-

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nary calculi, and until these are elucidated, we cannot hope that urinary lithiasis can be prevented.

Treatment of urinary stones in children is almost entirely surgical. The type of operation, of course, depends upon the requirements of the individual case. Even in the case of ureteral stone, cystoscopic manipulation is often impossible in children and ureterotomy should be performed at once. The surgical removal of the stone, however, does not discharge the obligation of the urologist and he should then look to prevention of recurrence. It is here that the proper diet and high vitamin A intake achieve great usefulness. These patients should receive a high vitamin, acid-ash type of diet, with the hope of forestalling recurrence of the calculi.

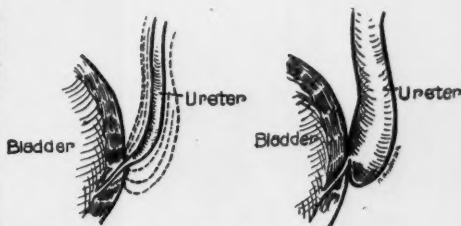


FIG. 11.—Schematic drawing, showing how dilatation of the ureter above a ureterovesical stricture may produce valve-like deformities.

### URINARY LESIONS OF CONGENITAL ORIGIN

*Hydronephrosis due to aberrant artery* is a relatively common disease and its recognition in childhood is a thing earnestly to be desired. Symptoms are not likely to appear early; the youngest patient we have encountered was a six-year-old boy. The incidence of aberrant renal arteries is, of course, much higher than that of cases in which there is a resultant hydronephrosis. It has been estimated that aberrant renal arteries are present in about 20 per cent of all persons. Only 20 per cent of these, however, are at the lower pole and hence capable of producing urinary obstruction.

The embryologic explanation of the occurrence of aberrant vessels is that the kidney in its ascent to its final location receives its blood supply from successive levels, with obliteration of each previous artery. Failure of this process at the final level allows the vessel to remain patent, and if it is situated at the lower pole, is capable of producing urinary obstruction.

It would not appear that ptosis of the kidney or inflammatory stricture must be presumed in order to explain the production of hydronephrosis in these cases. These aberrant arteries are always associated with fibrous peri-ureteral bands, also of congenital origin, and the combination constitutes a fixed point which inter-



FIGS. 12A and 12B.—The patient was a girl three and one-half years of age, who, when she was admitted to the hospital, complained of hematuria, chills, and fever. FIG. 12A (*left*). Retrograde pyelogram shows a filling defect in the lower pole of the right kidney. FIG. 12B (*right*). Photograph of specimen removed showing a Wilms' tumor, involving the lower half of the kidney.

feres with normal peristalsis. This results in gradual dilatation until finally the pelvis becomes redundant over this fixed point and this establishes a vicious cycle which increases the amount of obstruction (Fig. 4).

These cases are overlooked with striking frequency, a failure of recognition which is caused, I believe, by the usual absence of positive urinary findings. In fact, many of our patients with aberrant renal arteries have had perfectly clear urine. In a young person, persistent kidney pain, often most severe in the morning and waning through the day, with tenderness over the affected kidney, should always suggest the presence of this lesion. The pain is usually a dull aching and very seldom appears as colic. Gastro-intestinal symptoms may predominate. There is, of course, no way to make a positive clinical diagnosis without the aid of the roentgen ray. An intravenous urogram should be the first procedure and in almost every instance will yield a positive

## UROLOGIC PROBLEMS IN CHILDHOOD

diagnosis. Of course, the intravenous urogram is of no value in those cases in which kidney function has been completely destroyed (Figs. 5A, 5B, 6, and 7).

Surgical intervention is demanded when this condition is recognized, and if the patient is seen before extensive kidney destruction has taken place, a conservative operation may be employed. We have preferred the simple division of the artery with or without plication of the dilated pelvis and have had completely satisfactory results by this method. All too often, unfortunately, the process has gone beyond the stage at which the conservative operation will suffice, and nephrectomy is required. In our series of 29 cases, nephrectomy was necessary in 50 per cent of the cases in which operation was performed.

*Congenital megalo-ureter* is a term applied to a small group of cases with bilateral ureterectasis which occurs in the absence of lower urinary obstruction. These cases must be differentiated from those with congenital posterior urethral valves, hypertrophied verumontanum, etc. That the condition must be congenital is apparent from the very early age at which it has been recognized, together with the fact that it may occur in the absence of any obstructive lesion. The exact mechanism of its production is not clear but it would seem to be due to some congenital neuromuscular failure, with persistence of a fetal type of ureter. It differs from hydro-ureter in obstructive lesions in that the latter is associated with hypertrophy of the ureteral musculature and marked tortuosity, an evidence of hyperperistalsis.

Urinary infection usually is responsible for bringing these patients for medical attention and this may appear when the child is very young. Recurrent infection is the rule, until the true nature of the disease is finally disclosed by a complete urologic investigation. At this time cystoscopy reveals wide patulous ureteral orifices which allow bilateral ureteral reflux. Injection of a pyelographic medium shows widely dilated ureters which, in the later stages, may be somewhat tortuous. Oddly enough, the kidney pelvis often shows only moderate dilatation, not at all comparable to the extent of dilatation in the ureter.

The treatment of this condition constitutes a real problem. Operation is of no avail and the task is to control the infection. Drainage by inlying ureteral catheter may be necessary in the more severe acute phases of infection, and periodic lavage of the kidney pelvis is at times a useful procedure. I have always felt, however, that a minimum of instrumentation should be em-

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ployed, and that an attempt should be made to clear up the infection by means of a ketogenic diet and urinary antiseptics.

The prognosis in these cases is very bad and the patients almost never live to reach adulthood. There is a progressive kidney insufficiency, hastened by infection, and uremia is the terminal event (Figs. 8A and 8B).

*Ureterovesical stricture* presents quite a different problem in that a definite obstruction caused by a congenital stricture at the vesical end of the ureter is the cause of the ureterectasis. These strictures may be unilateral, as in the case presented here (Fig. 9), but bilateral lesions of this type also occur (Figs. 10A and 10B). Cystoscopic examination in these cases reveals a small ureteral orifice in contrast to the large patulous ureter of congenital megalo-ureter. An attempt at ureteral catheterization may be attended with some difficulty. Similar cases have been described as due to congenital valves in the ureter, and though this possibility must be granted, I have a feeling that many cases in which the condition is attributed to the presence of valves, simply represent the dilatation of the ureter above a stricture which results in a valve-like appearance (Fig. 11). It is true, of course, that this resulting deformity acts to increase the amount of obstruction already present.

Here again, it is the presence of infection which demands medical attention. The infection usually is ushered in by chills and fever, and varying degrees of kidney pain and tenderness are constant accompaniments. The finding of pus in the urine usually results in a diagnosis of pyelitis, but repeated incidents of this type finally bring the patient for thorough urologic study. The intravenous urogram usually suffices to determine the diagnosis. This shows a dilated ureter with constriction at the lower end and usually retention in the kidney an hour after injection of the dye. In some cases there may be delayed function and the differential phenolsulphonephthalein test shows diminished function on the affected side.

The treatment consists in the surgical relief of the obstruction. Good results may be expected if the process is not too far advanced. The ureter may not return to its normal size, but if drainage is free the patient will be well and no further kidney damage will result. In late neglected cases, ureteronephrectomy may be necessary.

## MALIGNANT TUMORS OF THE KIDNEY

Malignant neoplasms of the kidney in children present one of the most depressing problems in urology because there is so little



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we can claim to have accomplished for these poor unfortunates. Fortunately the incidence of these growths is not high, it having been estimated that only one child in 1,600 is affected by a kidney tumor. However, among malignant tumors occurring in children, 20 per cent are in the kidney and among all cases of kidney tumors, the incidence in children is about 12 per cent. At the Cleveland Clinic since 1920 we have records of 32 cases of kidney tumor in children, 16 of which have been verified by operation and pathologic examination.

It is not within the scope of this paper to discuss at length the theories regarding the pathogenesis or the pathology of these tumors, but a few remarks are pertinent to the subject. These growths are all mixed, undifferentiated tumors arising from embryonic tissue, and are characterized by very rapid growth. They present a varied pathologic picture and any one of a variety of forms may occur, depending upon the type of tissue which predominates. It is truly a problem of survival of the fittest and the strongest and most rapidly growing tissue elements take the field. This explains the many pathologic names applied to these tumors, but clinically they are a single entity, well known in their behavior, and may, from our standpoint, quite properly be grouped under one term — malignant kidney tumors of childhood.

These growths occur in very young children and have even been reported in fetuses and newborn infants. The vast majority make their appearance before the fifth year of life; some collected series show an incidence as high as 98 per cent, but in our group of cases only 70.8 per cent occurred in children under five years of age (Figs. 12A and 12B).

The presenting symptom or complaint is usually an abdominal tumor which has appeared rather suddenly and has grown rapidly. The longest history we obtained was of six months' duration and this patient had a very large inoperable tumor. Chills and fever are not uncommon and pain is a frequent complaint. Hematuria is a relatively infrequent symptom and occurred in only two of our cases.

The diagnosis usually offers no difficulty when one considers that about 90 per cent of the patients present themselves with a palpable tumor mass in the kidney region. Kidney tumor is by far the most common cause of a large tumor mass in a child. In the remaining 10 per cent of cases, hematuria, kidney pain, and the symptoms of urinary infection should direct one's attention to the urinary tract and further investigation and pyelograms disclose the true nature of the disease.

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The results of treatment of these tumors must impress all who have seen any number of these cases as very discouraging. No matter what treatment is adopted, that is, operation, irradiation, or both, the outcome is nearly always fatal and this usually within a very short time. It is truly remarkable to see how some of these large tumors melt under irradiation therapy like fat before the fire, but this, unfortunately, does not improve the prognosis, for they recur rapidly and become more radioresistant.

## TREATMENT OF CERTAIN FRACTURES OF THE PATELLA

JAMES A. DICKSON, M.D.

In the literature sufficient attention has not been given to a special type of treatment of transverse and comminuted fractures of the patella in which one large fragment is intact and there are one or more smaller fragments. The only discussion of this subject, to my knowledge, has been that by Thomson at the meeting of the American Medical Association in June, 1934. Much has been written about the importance of insertion of sutures of kangaroo tendon or of fascia to prevent not only the horizontal separation of the fragments, but to prevent also any tilting of one fragment on the other. Practically nothing has been said about the removal of the smaller fragments and the substitution of tendinous and fascial repair for bony union. I have used this procedure for a number of years with such extremely satisfactory results including the elimination of many of the difficulties ordinarily associated with this type of fracture that I feel that a reference to this procedure is warranted at this time.

The keynote of the treatment of injury of the extensor apparatus of the knee is the restoration of the extensor power without impairment of flexion. The patella is simply a sesamoid bone lying at the point of the tendinous insertion of the great extensor muscle of the thigh (the quadriceps). The significance of a fractured patella depends largely on the loss of the continuity of the tendon; and the success or failure of treatment depends on the restoration of the function of the tendon. If the tendon is properly repaired, it really does not matter whether the patella is only half or two-thirds of its original size. Hence it would appear that there should be no disadvantage in the removal of the comminuted fragments so long as the tendon and the lateral expansions of the capsule are meticulously repaired. This assumption, indeed, has been borne out by clinical experience.

I have adopted the following procedure for the treatment of these fractures of the patella. Usually it is advisable to wait from two to four days after the injury has been received before the operation is performed. During this period the knee is splinted in extension with or without traction, and ice caps are applied. Aspiration of fluid from the knee joint often is helpful if much hemorrhage has occurred.

After suitable preparation, the patella is explored under either spinal or general anesthesia. The application of a tourniquet may greatly facilitate the operation.

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A curved longitudinal incision is made and the tissues are reflected to give complete exposure of the joint. The fracture is explored and the blood clots are removed. The smaller fragments of the patella are dissected free from the tendon and then the tendon is attached to the patella by loops of fascia from the same leg. These are passed through the tendon and fastened into either the patella or its capsule.

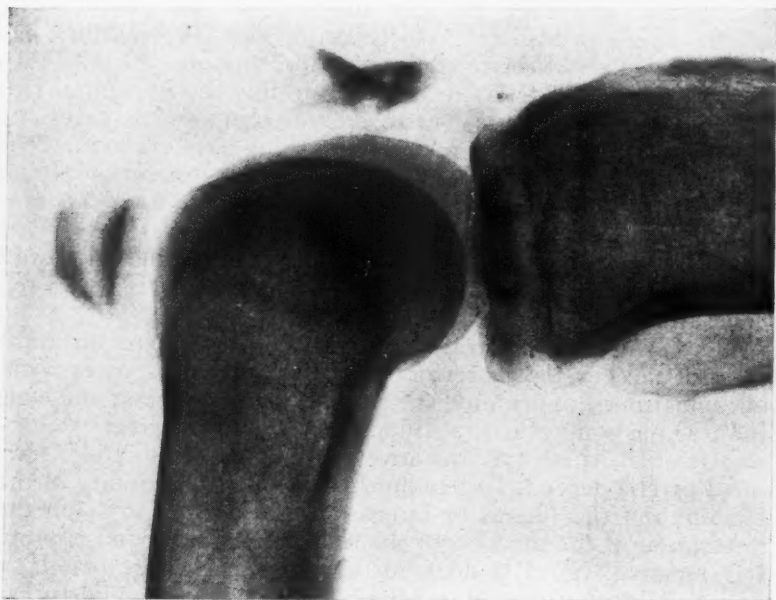


FIG. 1.—Roentgenogram showing comminution of lower third of patella following an automobile accident.

Care should be taken not to shorten the patellar ligament in this process or a much longer time may be required to procure full and normal motion. There are many ways in which the fascia or sutures may be applied and each surgeon usually has some modification that satisfies his individual fancy. The lateral expansions of the torn capsule are then carefully sutured.

The advantages of this procedure are that active motion of the knee can be restored much sooner as dependence is placed on a fascial and not a bony repair. Early motion of the joint is certainly desirable and this can be accomplished without the danger of disturbing any bony union. It has been shown by Scudder and Miller<sup>1</sup> that in 19 per cent of the cases of fracture of the patella

## TREATMENT OF CERTAIN FRACTURES OF THE PATELLA

absolutely no bony union developed, yet good functional results were reported. Therefore, if good results were obtained in such a large proportion of cases with fibrous union, it certainly suggests the advantage of depending only upon the repair of the tendon, for this facilitates the early motion of the joint. Occasionally permanent loss of motion has been reported as the result of long immobilization. Early movement is essential for good functional results and hence the advantage of the operation for repair of the tendon is obvious.

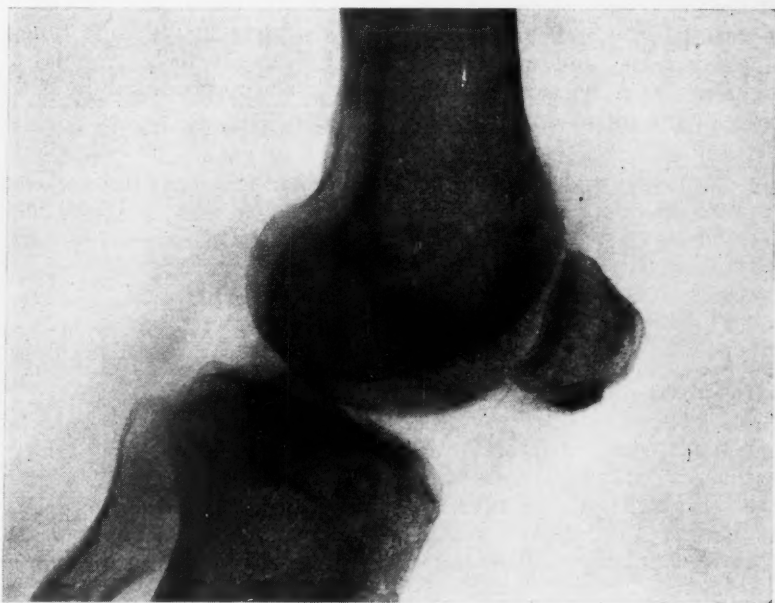


FIG. 2.—Roentgenogram made ten weeks after operation showing the repair. There was normal function in the knee joint.

An additional advantage of this procedure is that there is no possibility of producing an irregular under-surface of the patella which would lead to pain and loss of motion in the knee. The constant movement with the accompanying friction produced by such a rough area may result in arthritic changes and long disability.

No matter how great care is taken to approximate the fragments, it is extremely difficult to avoid this irregularity.

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In the postoperative treatment it is necessary to emphasize the importance of voluntary efforts on the part of the patient to re-establish the function of the quadriceps. Massage and electrical treatments are beneficial but their value cannot be compared with that of the patient's own efforts.

SUMMARY

The advantages of a simple operation for fracture of the patella, in which the bony fragments are removed and the emphasis is placed on repair of the tendon, include the possibility of early mobilization which greatly enhances the chances for good functional results, and elimination of the danger of a traumatic arthritis from friction of the rough surfaces produced by the patellar fragments.

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## INTRACRANIAL OPERATIONS IN THE SITTING POSITION \*

W. JAMES GARDNER, M.D.

During the last four years, a majority of the major intracranial operations at the Cleveland Clinic have been performed with the patient in the sitting position. This position has been found to possess many very definite advantages and also certain disadvantages. The idea of placing the patient in the erect posture for craniotomy is not new, and no claim is made for originality in any of the observations to be described. Frazier<sup>1</sup> early appreciated the advantages of the erect posture in operations on the sensory root of the fifth nerve. In several of his communications on trigeminal neuralgia he has stated that in this position there is less bleeding, the patient requires less ether, and the field of operation is on a level with the eyes of the operator, which facilitates exposure. For many years de Martel<sup>2</sup> has advocated having the patient in the sitting position during intracranial operations. He has employed this method since 1911, and has found that elevation of the patient's head decreases hemorrhage and aids respiration. On account of the greater likelihood of syncope in this position, he favors local anesthesia, which allows earlier recognition of the syncope which can be combated by lowering the patient's head.

In 1930, I began to place the patient in the sitting position for operations on tumors of the cerebellum, with the hope of overcoming certain difficulties, such as the respiratory embarrassment, and also the occasional tendency for the cerebellum to bulge through the craniotomy opening. The cerebellar head rest was attached to the arms of a dental chair, and several operations upon the cerebellum were carried out in this position. After a trial extending over several months, the advantages were so obvious that alterations were made in the head rest so that supratentorial tumors could be attacked with the patient in the same posture. In the last three years, I have reverted to the use of the prone position in only one case of suboccipital craniectomy. This patient was a woman, aged seventy-six years, whose ninth nerve was sectioned for glossopharyngeal neuralgia.

From our experience with this position, its advantages over the horizontal position may be enumerated as follows: (1) There is a reduction of intracranial venous pressure resulting in diminished bleeding, lowering of intracranial pressure and a lessened tendency to cerebral oedema consequent to operative manipula-

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W. JAMES GARDNER

tions; (2) freedom from respiratory embarrassment; and (3) easier access to the patient for the anesthetist, as well as the operator. The disadvantages of this position are: (1) occasionally a patient goes rapidly into profound shock; and (2) the lowered intracranial venous pressure may favor air embolism, if a dural sinus is opened.

The reduction of the intracranial venous pressure, of course, is the result of the improvement in venous return which occurs on elevation of the head. It is due partly to the pull of the column of blood from the brain to the right side of the heart and partly to a lowered intrathoracic pressure. To anyone who has observed



FIG. 1.—Patient in position for a suboccipital craniectomy or cervical laminectomy. The head rest is lined with sponge rubber and is adjusted to the contour of the patient's face.

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operations with the patient in the erect, as compared with the horizontal position, the diminution of venous bleeding and the ease of its control in the former cannot help but be apparent. The reduction of the intracranial pressure is the most striking and significant advantage gained by elevation of the patient's head. This, of course, is secondary to the reduction of the intracranial



FIG. 2.—The exposure for resection of the fifth and ninth cranial nerves and second and third cervical posterior roots on the right side for relief of pain from carcinoma. Illustration shows the ease of exposure of the eighth nerve and angle. Combined hemisuboccipital craniectomy and hemilaminectomy.

venous pressure. This reduction in pressure can be measured by performing a cisternal or ventricular puncture and recording the pressure in the same patient in both the horizontal and sitting positions. If the intracranial pressure is below 150 millimetres of water in the horizontal position, it will be subatmospheric in the erect posture. If the intracranial pressure is greatly increased in

the horizontal position, it will be found to be at least 200 millimetres lower than when the patient is sitting erect.

When the patient is sitting upright, except in the case of severe intracranial pressure, there is no significant herniation of the brain when the dura is opened. With this reduction of herniation, intracranial exploration can be more thorough and extirpation of the tumor is rendered more simple. Because the tumor can be removed with less trauma and less retraction, immediate cerebral oedema is reduced to a minimum. In no case of cerebral tumor in which the operation was performed with the patient in the erect posture, has it been necessary to sacrifice the bone flap on account of herniation of the brain.

As de Martel has stated, "the sitting position favors easy respiration and is the position all patients instinctively assume when respiration is labored." Certain patients who tend to breathe stertorously when lying horizontally, breathe quietly and without effort in the sitting posture, and also the head can be flexed more without a tendency to stertorous breathing. This is a point of considerable importance in the attack on a cerebellar tumor.

When a brain tumor is removed, a procedure which is likely to be slow and tedious, it is decidedly advantageous that the various members of the operating team are comfortable and have easy access to the patient. This is especially true of the anæsthetist. With the patient in the sitting position, the anæsthetist is not required to sit under a tent of draperies, and therefore has a better opportunity to observe the patient's condition and to minister to his needs. In addition, the patient's arms are available for intravenous medication or for transfusion, should this prove necessary.

In a series of fifty-six suboccipital craniectomy operations, no distinct disadvantages of the sitting position have appeared. These patients have shown no fall in blood-pressure which could not be combated by hypodermic stimulation or intravenous fluids. In operations on the cerebral hemispheres, however, the story is different. The sitting position, of course, would not be desirable or feasible in operations on tumors arising from the floor of the anterior or middle cranial fossæ or from the sellar region. With the operative field in these situations, it would be necessary to lift the brain away from the lesions and against the force of gravity. The sitting position, therefore, is not employed when a tumor is suspected on the inferior surface of the cerebral hemisphere. In the past four years, seventy-eight craniotomies other than suboccipital, have been performed with the patient in the sitting

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position, as compared with 147 similar operations using the supine position. In this series of seventy-eight cases, a rapid and profound shock appeared in two instances and was accompanied by visible air emboli in the cerebral vessels. Both of these patients were past sixty years of age, had cerebral arteriosclerosis and



FIG. 3.—Position for frontal or lateral craniotomy. After the field is prepared and the line of the incision marked, the head is fastened to the head-rest with a strip of adhesive.

arterial hypotension, and the lesion in each case was a parasagittal meningioma. In one of these, the sudden syncope undoubtedly contributed to a fatal termination. This patient also had severe asthma and emphysema. Since these experiences, I have not em-

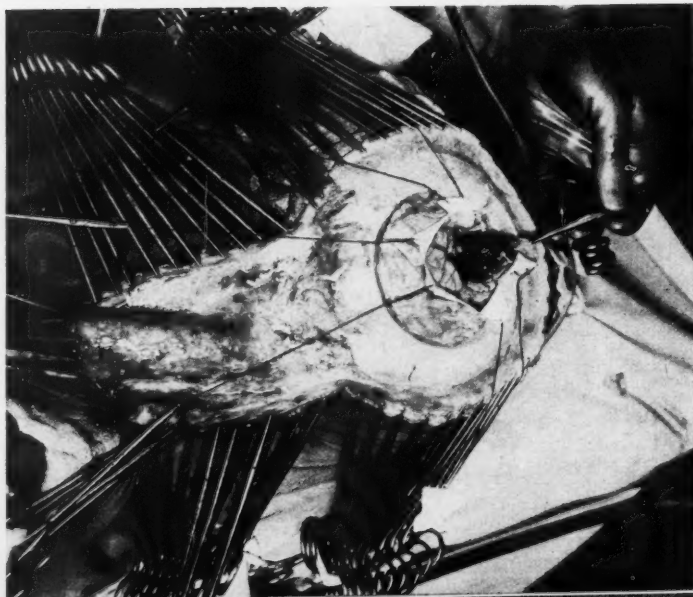


FIG. 4.—Removal of a left parasagittal meningioma. With the patient in the sitting position, the brain retracts by its own weight.



FIG. 5.—Removal of a similar, though smaller, tumor from the right parasagittal region with the patient in the horizontal decubitus. The bulging brain is being retracted from the tumor.



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played the sitting posture in operations upon elderly or arteriosclerotic subjects, particularly when there is an associated hypotension.

De Martel stresses the advisability of employing local anæsthesia when the patient is in the sitting posture, in order to permit earlier recognition of threatened syncope. When this complication occurs, he immediately lowers the head. The chair which he employs permits rapid lowering of the head during the course of an operation. Thus far, I have not been able to incorporate this desirable feature in our equipment. Given a chair with this feature, I believe that the last valid objection to this position would be eliminated.

I do not agree with de Martel's dictum regarding the necessity for local anæsthesia, although it is perfectly true that with local anæsthesia syncope is more readily recognized. But there can be no question also that general anæsthesia, probably by elimination of the psychical factor, reduces very materially the incidence of syncope, and I feel that this reduction in frequency by far outweighs the advantage of its earlier recognition under local anæsthesia. The importance of the psychical factor in syncope is well illustrated by its quite frequent occurrence in encephalography under local, as compared with its rare occurrence under general anæsthesia. Since 1930, I have preferred to use avertin in cranial surgery. In preparation, the patient receives a hypodermic injection of codeine and scopolamine one hour before operation, followed forty minutes later by the instillation into the rectum of 50 to 100 milligrams of avertin per kilo of body weight.

The objection has been raised that the sitting position in craniotomy may favor the occurrence of post-operative hæmorrhage. In the fifty-six cases of suboccipital craniectomy, a post-operative hæmorrhage was not detected clinically or at necropsy in any case. There was likewise no post-operative hæmorrhage in fifty-one operations for resection of the sensory root of the fifth nerve by the temporal approach. Following seventy-eight craniotomies with the patient in the sitting position, a post-operative hæmorrhage occurred in three instances. This incidence of hæmorrhage is considerably higher than in the series of 147 craniotomies carried out with the patients in the horizontal position, in which there was only one post-operative hæmorrhage. On analyzing these cases, however, it was found that post-operative hæmorrhage occurred only in cases of jacksonian epilepsy in which there was no increase in intracranial pressure. In my experience, this type of case is notorious for its high incidence of

post-operative hæmorrhage. Hence the more frequent recording of this complication after operations with the patient in the sitting, as compared with the horizontal position in our series, might be explained by the fact that most patients with jacksonian epilepsy are operated upon in the sitting position. I do not believe that the erect posture during operation favors the occurrence of post-operative hæmorrhage.

The sitting posture is employed routinely in encephalography and in ventriculography. It has also been used in twenty-nine cases of laminectomy on the cervical or upper dorsal spine and in nine operations for removal of the cervicodorsal sympathetic ganglia by the Adson approach. This latter operation, in my experience, is definitely simplified by this technic. In the case of laminectomy, the position is of great value, provided a general anæsthetic is used. In cordotomy when performed under local anæsthesia, in this position, the patient frequently experiences a syncopal attack after the dura is opened. This is caused by the ascent of air into the cerebral subarachnoid spaces. Under general anæsthesia, no significant change occurs when the dura is opened.

The value of the sitting position was strikingly demonstrated recently in the case of a patient with a meningioma at the level of the foramen magnum. This patient had a quadriplegia, the diaphragm was paralyzed and the intercostal muscles were very weak. For this reason, the respirations were shallow and rapid and there was mild cyanosis. This patient obviously would not have tolerated the prone position, but she withstood the operation splendidly in the sitting position and had an uncomplicated convalescence.

#### SUMMARY AND CONCLUSIONS

The sitting position of the patient, combined with avertin anæsthesia, is recommended for operations on the cerebellum. This position results in (1) a diminution in bleeding, (2) a lowering of intracranial pressure, (3) a lessened tendency to immediate cerebral oedema, (4) an improved respiratory exchange, and (5) it also facilitates access to the patient, particularly by the anæsthetist. This position is not recommended for operations on tumors about the sella turcica or on the inferior surfaces of the cerebral hemispheres. In other cerebral tumors, the position is recommended with reservation because of the tendency for an occasional patient to go into prompt and profound shock. The position has distinct advantages in cervical and upper dorsal laminectomy and in excision of the cervicodorsal sympathetic ganglia by the Adson approach. It does not predispose to post-operative hæmorrhage.

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## INDUCED ULTRAVIOLET FLUORESCENCE AND ITS RELEASE BY VISIBLE LIGHT \*

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In the course of investigations on the detection of induced radioactivity and of extremely weak ultraviolet radiation we have recently observed that the ultraviolet fluorescence of certain substances following their exposure to and their removal from röntgen or gamma-irradiation persists for unexpectedly long periods of time. This ultraviolet fluorescence, furthermore, is conspicuously increased if the irradiated compounds be exposed to visible light. This is in agreement with an observation made by W. Kudrjawzewa.<sup>1</sup>

Of twenty-five compounds we have thus far examined sodium chloride, potassium chloride, rocksalt and fluorite crystals exhibit these effects most clearly. Impurities inhibit, but previously repeated recrystallization facilitates the subsequent induction of ultraviolet fluorescence. Heating the crystals impairs their fluorescence which, indeed, is completely stopped by dissolving the compounds in distilled water.

A photoelectric Geiger-Muller-counter tube equipped with a cadmium electrode and a quartz window has been used for measuring the ultraviolet fluorescence. This counter is very sensitive to ultraviolet radiation and hardly responds to visible light. The ultraviolet light has also been registered by means of the darkening produced on Eastman hypersensitive panchromatic dry plates.

The fluorescent effects described have been elicited in the following way: Samples of crystals were exposed to radon (100 millicuries,  $1\frac{1}{2}$  mm. brass filter, close distance) or to röntgen rays (200 kv, cardboard filter, 40 cm focal distance, 25 r-min.) for periods of time ranging from a few seconds to ten hours. A few particles thus irradiated cause discharges in the Geiger counter; in general, the number of counts is proportional to the intensity and to the duration of the primary irradiation; but, in each case, it is found that illumination by visible light at once results in a tremendous increase of the counts. Thus, samples primarily irradiated for only a few seconds may require the stimulus of visible light before their acquired property of ultraviolet fluorescence becomes demonstrable with the counter. On the other hand, samples irradiated for several hours produce counter discharges in the dark even though they be removed from the counter window by as much as one meter. In this case, illumination by

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visible light so greatly increases the number of counts that satisfactory observations can only be made by placing the irradiated substance several meters from the window.

The counter discharges are completely stopped when a thin glass plate, 0.2 mm. thick, is interposed between the material and the counter window. Spectrographic examination by means of a Leiss quartz monochromator in the case of sodium chloride, shows that the emitted radiation has one maximum in the neighborhood of 2450A. This agrees with Kudrjawzewa's<sup>1</sup> findings and is also of interest because J. O. Perrine<sup>2</sup> demonstrated that sodium chloride fluoresces in this same region as long as the substance is directly exposed to röntgen rays.

The ultraviolet fluorescence subsequent to primary gamma or röntgen irradiation, undergoes decay, very likely to the exponential type. The half-life of induced ultraviolet fluorescence ranges from a few minutes to many days depending upon the intensity and duration of exposure to the primary source of irradiation. The half-life, furthermore, is shortened if the substance is illuminated by visible light, which, if sufficiently intense, completely stops the emission of ultraviolet light, although the latter may again be detected after the substance has been allowed to rest in the dark.

The response to visible light is, moreover, characterized by lag, which increases as decay progresses. There is almost no measurable lag following either the onset or the cessation of visible illumination during the early life of induced ultraviolet fluorescence. But, lag in both respects becomes more prominent as time, measured from the moment at which the substance is removed from exposure to the primary radiation, continues to elapse.

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## THE MEDICAL MANAGEMENT OF URINARY LITHIASIS

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In certain countries, the incidence of urinary calculi varies considerably. In Great Britain "stone areas" are well recognized; urinary calculi occur more frequently along the east coast, and in parts of Derbyshire and in North Wales. Joly<sup>1</sup> stated that in the east and southeast of France, kidney and bladder stones are prevalent but are found infrequently in Normandy. In Africa, urinary calculi frequently occur in the region of the lower but not of the upper part of Egypt. The relationship of bilharziasis to the frequency of calculi and the variation in the two regions was investigated by Pfister<sup>2</sup> who stated that the ova formed the nucleus for stones in approximately 10 per cent of the cases. Holmes and Coplan<sup>3</sup> made an intensive study as to the prevalence of urinary calculi in the various sections of this country. From personal communications with urologists throughout the United States, they concluded that calculi occurred more frequently in southern Florida and in southern California than in other parts of the country.

In 1931 McCarrison<sup>4</sup> stated that in some regions in India, stones were so prevalent among the populace that these places were designated as "stone areas," while in other localities, they were encountered but rarely. McCarrison observed the frequent occurrence of stones in regions in which there was not proper balance of food constituents in the diet.

Fujimaki<sup>5</sup>, under the supervision of Dr. Saiki, while investigating the vitamin content of food materials, observed the frequency of the occurrence of bladder and renal calculi in rats maintained for a long period of time on a diet either lacking or deficient in vitamin A.

Fujimaki<sup>5</sup> in 1926 reported the results of his experiments upon rats fed for varying intervals of time upon a vitamin A deficient diet. He demonstrated conclusively that calculi could be formed by this means. In 1917 Osborne and Mendel<sup>6</sup> found 81 cases of urinary calculi in the course of necropsy investigation of 857 rats. Of this group, 35 rats or 43 per cent had never received butter fat or any other food containing vitamin A. Upon further investigation, they noted that in every instance in which urinary calculi were found, the rats had been without an adequate amount of vitamin A at some time during the experiments.



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In addition to these experimental data, there are many clinical observations that lead us to presume a definite relationship between faulty diet and the development of urinary calculi.

According to the literature, the presence of vesical calculi in children was quite common in England and France fifty years ago. In England, Thompson<sup>7</sup> collected 2583 cases of urinary calculi of which 1281 cases occurred in children under sixteen years of age. Later, Joly<sup>1</sup> reviewed 536 cases of urinary calculi taken from the records of St. Peter's Hospital from 1915 to 1924, and he emphasized the marked decrease in the incidence of urinary calculi in English children during recent years. The same observations have been made by Desnos and Minet<sup>8</sup> in France.

In 1900, however, Assendelft<sup>9</sup> reviewed 630 cases of vesical calculi seen in various Russian hospitals and reported that 77 per cent occurred in children under ten years of age, and that 86.5 per cent occurred in young persons under twenty years of age.

Such statistics show that there can be little doubt but that the occurrence of vesical calculi in children has diminished markedly in countries in which training in nutrition and hygiene has received attention. In countries where better standards of living and dietary regulations have not been emphasized, urinary calculi are still frequently observed in children.

In view of the apparent relationship existing between the improper balance of the daily diet and the development of urinary calculi, certain experiments were performed in an effort to elucidate the problem, and these investigations have been reported in previous communications.<sup>10,11</sup>

Urinary calculi developed in a high proportion of albino rats which were maintained on a diet deficient in vitamin A. When this deficiency in the diet was continued for a period of 250 days, vesical calculi developed in 85 per cent of the experimental animals, and renal calculi developed in 42 per cent. The calculi thus produced were light brown, spherical, and varied in size from 0.5 to 8 mm. in diameter. They were composed chiefly of calcium phosphate, and a small amount of mucoid substance and traces of carbonates were present. Neither oxalates nor uric acid were detected.

Three constant findings which might be associated with the formation of calculi were present in these experimental animals. They were (1) keratinization of the epithelium of the genito-urinary tract; (2) the presence of infection in the genito-urinary tract; and (3) the presence of alkalinuria.

The *keratinization of the epithelium of the genito-urinary tract* was noticed after the diet had been deficient in vitamin A for a period of from eight to ten weeks. This finding was not confined to the genito-urinary tract, but involved other mucous membranes also.

This experimental finding is in accordance with the clinical observations of Wilson and Du Bois<sup>12</sup>, who, in 1923, noticed the presence of keratinization of the epithelium of the trachea, bronchi and other mucous membranes in infants who died as the result of infection associated with vitamin A deficiency. Similar observations were made by Mori<sup>13</sup>, Blackfan and Wolbach<sup>14</sup>, and others.

*Infection in the genito-urinary tract* developed in a large proportion of rats maintained on a diet which was deficient in vitamin A for a long period of time. Infection of the bladder occurred usually after thirty days, and renal infection occurred after a period of from sixty to ninety days. When the experiment had progressed from 200 to 250 days, infection of the bladder was present in 72 per cent of the rats, and in 42 per cent of these a co-existing renal infection was present.

Streptococci, staphylococci, and mixed cultures were the organisms found most frequently.

*Alkalinuria* was a constant finding when the rats were maintained on the diet deficient in vitamin A. By the addition to the diet of vitamin A alone, the urine reaction became acid.

#### SOLUTION OF URINARY CALCULI

It has likewise been demonstrated that, by the addition to the diet of vitamin A alone, the formation of calculi can be prevented. In order to determine whether stones which already were present might be dissolved by the administration of vitamin A, observations were made on thirty rats in which bladder or renal calculi were present. Except for the addition of cod liver oil, the diet remained the same as that by which the calculi had been produced. In every instance the stones disappeared during periods which varied from 50 to 107 days.

In those rats in which a pronounced infection was present, a longer period of time was required for the solution of the calculi than was required in those animals in which an infection was not present. Thus, by experimental investigations, we proved that if white rats were maintained on a diet deficient in vitamin A for a sufficient period of time, urinary calculi could be produced; and that, by the restoration of vitamin A to the diet, these calculi could be dissolved and made to disappear.

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### APPLICATION OF ABOVE FINDINGS TO CLINICAL CASES

During the past year, a selected group of patients, in whom urinary calculi were present, has been treated by means of a dietary regimen in order to ascertain whether observations made in the experimental laboratory might be applied to clinical cases.

It is obvious that all patients suffering from urinary calculi can not be treated by conservative measures. If the calculus is producing a definite obstruction and thereby causing further damage of the renal parenchyma and impairing the renal function, it may not be advisable to temporize with medical treatment when by surgical intervention the obstruction may be relieved immediately and thus prevent the further injury of the kidney tissues.

During the past year, dietary treatment has been used in the following groups of cases:

1. Those in which the patients refused to have the calculus removed by surgery;
2. Those in which calculi were present in one of the calices of the kidney, but were not producing obstruction;
3. Those in which small calculi were present in the renal pelvis but were not producing obstruction;
4. Those in which bilateral renal calculi were present but in which surgical intervention was not deemed advisable;
5. Those in which we desired to prevent the recurrence of calculi following removal of stones by operation;
6. Those in which calculi were of sufficient size to require treatment by nephrectomy;
7. Those in which calculi were passed at frequent intervals but could not be demonstrated roentgenographically;
8. Those in which elderly patients who had fractures or osteomyelitis were required to remain in a recumbent position for a long period of time.

Before a diet may be prescribed, certain urologic observations are essential. Our procedures are as follows:

A roentgenogram of the kidneys, ureters, and bladder is first made to determine whether or not a calculus is present. This is followed by an intravenous urogram to determine the location of the calculus in the kidney, and to determine whether the calculus is obstructing the passage of urine from the kidney itself. The urogram may also reveal the presence of a non-opaque stone and is of additional value in indicating an estimation of the function of each kidney.

A cystoscopic examination is then made to ascertain the function of each kidney by means of the phenosulphonephthalein

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test. Samples of the urine from each kidney and from the bladder are taken for the determination of the hydrogen concentration, bacteriologic culture and routine study.

Blood chemistry studies are also of utmost importance. Determinations of blood urea, creatinin, sugar, uric acid, calcium, phosphorus and phosphatase are made in each case. These studies are of extreme importance in cases in which calculi of the uric acid type are present and also in those in which changes in the blood calcium and blood phosphorus may indicate the presence of parathyroid disturbances.

If calculi have been passed previously and the specimen is available, it is examined in our chemistry laboratory.

The patient is hospitalized for a period of from three to seven days in order that he may grasp the full significance of the diet, that he may have a thorough understanding of the principles involved, and that he may be instructed regarding the routine to be followed after he has left the hospital. Our dietitian visits the patient daily to explain the details of the diet and to furnish and discuss sample menus. With this instruction, the patient, within a short period of time, can prepare his meals with a remarkable degree of accuracy.

As a general rule, in the absence of infection, the high vitamin A acid-ash diet is sufficient to render the reaction of the urine strongly acid; but in patients in whom an infection such as the proteus organism is present, an acidifying agent must be added to the prescribed diet. This is usually given in the form of sodium acid phosphate in capsules or ammonium chloride in enteric coated tablets. It is important that the pH of the urine be kept between 5 and 5.4, and the medication necessary to maintain this level can be determined while the patient is in the hospital. The pH determinations are made daily under similar conditions. The first morning specimen of urine is discarded and the specimen voided just before breakfast is sent to the laboratory for examination. By this routine the effect of awakening respiratory changes on the pH of the urine are eliminated and the effect of the alkaline tide is avoided.

Just as the blood sugar determination is of value in the management of a patient with diabetes, the determination of the pH of the urine is of value in the management of a patient with urinary lithiasis. In each case, also, the patient must rigidly follow his prescribed diet. The patient is instructed concerning the method for making his own pH determination and a very simple, inexpensive apparatus\* may be procured for this purpose. The

\*We recommend the apparatus manufactured by the La Motte Chemical Products Company.

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patient makes the determination daily and presents a chart to his physician at regular intervals. In this way the physician can determine whether the dosage of sodium acid phosphate or of ammonium chloride must be increased or decreased. Consultation and advice from the family physician is required frequently and the patient should report for observation at regular intervals. The diet and medication must be followed exactly without any alteration, unless the physician advises some change.

### CLINICAL OBSERVATIONS

Since these clinical investigations have been undertaken, it has been a routine procedure at the Cleveland Clinic during the past two years to prescribe an acid-ash diet high in vitamin A in all cases in which urinary calculi have been removed. Other therapeutic measures such as eradication of renal infection, or elimination of stasis in the urinary tract have not been neglected.

During this time, only one patient has had a recurrent calculus following the removal of a stone from the lower portion of the right ureter. An associated infection and hydronephrosis of the right kidney were also present in this case. Following the operation, the patient neither followed instructions nor reported for post-operative therapy, and one year later a large calculus was present in the pelvis of the right kidney.

From our observations thus far, we are most optimistic regarding the efficacy of this regimen as a prophylactic measure against the recurrence of urinary calculi.

### END RESULTS

At the present time, we have a series of twenty-one cases in which renal calculi have undergone complete solution. In this series of cases, stones have been present which varied in size from a small calculus in a calyx of the kidney to large stones in the kidney pelvis.

In a larger group of patients who have been placed on this dietary regimen, there has been a definite diminution in the size of the calculi, but insufficient time has elapsed for complete disintegration to take place.

In a group of 11 patients, all of whom happen to be physicians, the histories state that calculi had been passed at frequent intervals. After the institution of medical treatment, all of these patients have been free from symptoms for a period of 18 months. Although this series of cases is too small, and insufficient time has elapsed to permit definite conclusions to be drawn regarding the clinical application of this method, the outlook for the med-

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ical treatment of urinary calculi seems exceedingly hopeful in selected cases in which urinary calculi are present.

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## TREATMENT OF THE GASTRO-INTESTINAL TRACT IN CHRONIC RHEUMATOID ARTHRITIS \*

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Rheumatoid arthritis still remains one of the great therapeutic problems of the age. Etiologic factors are still indefinite, although infection and the allergic reaction to infection seem the most logical explanation at the present time, but these do not seem to explain satisfactorily all the peculiarities and complexities of this disabling disease. Until the time when the cause and treatment of this moot problem is generally understood and agreed upon by the students and investigators of rheumatoid arthritis, research must continue its endeavor to unravel the mystery. The present study was undertaken to determine what, if any, evidence could be found in the digestive tract of these patients which might be of value in the solution of this therapeutic problem.

Evidence has been accumulating for some time that points to a possible role of the gastro-intestinal tract in arthritis. Constipation and colon dysfunction are such frequent accompanying symptoms that Lane<sup>1</sup> went so far as to advise colectomy to remove the intestinal stasis which he considered the cause of arthritis. Unfortunately, this work was marred by over-enthusiasm. Rare indeed is the arthritic patient who has not gone through a siege of drastic and unphysiologic purging and not infrequently at the doctor's suggestion.

The gastro-intestinal tract has also received much attention through the possible role that diet might play in arthritis. Protein, carbohydrates, various combinations of food and most recently the vitamins have been duly incriminated. Granted that most of this has been pure theory, and all too frequently the theory of a cult or quack, the evidence must be included to show the trend of thought about this disease. The most scientific thought along dietary lines is the work of Pemberton<sup>2</sup>, who advocates a low carbohydrate diet. This is based on the finding of a decreased glucose tolerance in these patients, and the belief that the intake of sugar should be restricted, because the tissues do not utilize sugar properly.

Goldthwaite and Osgood<sup>3</sup> have also emphasized the importance of proper function and elimination of the gastro-intestinal tract in the treatment of rheumatoid arthritis. They call attention chiefly to the asthenic and ptotic condition of the gastro-intestinal tract, due to the poor posture of the patient, and advo-

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cate physiotherapy, especially corrective exercises, to improve nutrition and metabolism.

The gastric secretions have been found to be diminished, or absent, in many cases of arthritis and Pemberton<sup>4</sup>, of Liverpool, treated his patients almost exclusively with large doses of hydrochloric acid. It was my pleasure to see a whole ward of his patients taking very large doses of dilute hydrochloric acid, 8 to 12 dr. daily, and getting along about as well as any of these patients do. He also used a diet low in carbohydrate.

Fletcher and Graham<sup>5</sup> have approached the problem presented by the gastro-intestinal factor in arthritis in still a different manner. In 65 per cent of their patients there was an atonic condition of all or some part of the colon. McCarrison reproduced such colons by feeding animals diets high in carbohydrate and with low vitamin content, especially lacking in vitamin B. Fletcher and Graham therefore suggest that the arthritis is secondary to the disease in the colon, and treat their patients accordingly by decreasing the carbohydrate and increasing the vitamin B intake. With this treatment they are able to show marked improvement both in the colon and joint condition.

These various views suggest some relation of disorders of the gastro-intestinal tract to arthritis and we chose to study the question by an analysis of 100 consecutive cases of rheumatoid arthritis in all stages, from the mildest case to the patient confined to a wheel chair. It has been routine procedure in our clinic to have a gastric analysis and a complete gastro-intestinal roentgenological study on each patient, when possible. Hence these examinations were not limited to those patients who complained of gastro-intestinal symptoms. We attempted to study each case from the standpoint of the history of digestive abnormalities, the diet, the state of nutrition, the role of infection in the gall bladder, appendix and diverticula, if present, the result of removal of such infection when performed during the course of the disease, the gastric secretory findings, the roentgen findings and the effect of treatment on the course of the disease and on the gastro-intestinal conditions present.

Only twenty-four patients of the series had gastro-intestinal complaints aside from constipation. Sixty-one had severe constipation for which they were using almost daily laxatives or enemas. Twenty-six had no gastro-intestinal complaints.

The dietary factor was difficult to evaluate in these cases. In general the diet was inadequate, but no definite deficiency could be demonstrated with the exception that the protein intake was

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low in the majority of instances. The intake of carbohydrate had not been excessive, so far as we could determine. The nutrition was almost universally poor, and had been for a long time before the onset of symptoms. Exhaustion and fatigue were almost the universal rule. Little or no evidence was elicited to suggest that focal infection in the gall bladder, appendix or diverticula might be a factor. A very small percentage of patients displayed evidence of disease in these organs and only four were subjected to abdominal operations after the onset of the arthritis; in none of these was there demonstrable relief of symptoms.

The gastric analysis showed more definite deviation from the normal. In eight cases there was no record of any test. Three patients had hyperacidity, nineteen had normal acidity, forty-seven showed hypoacidity and in twenty-three, there was achlorhydria. The percentage of these patients with acid deficiency is considerably higher than that usually found in patients of similar age, that is thirty to forty-five years.

The x-ray findings showed still more deviation from the normal. In four cases no roentgenographic examination was done. The following gastro-intestinal abnormalities were reported in the remaining ninety-six patients:

Marked dilatation of stomach.....	1
Duodenal ulcer.....	2
Dilated duodenum.....	3
Non-functioning gall bladder.....	10
Gall stones.....	4
Chronic appendicitis.....	4
Inverted cecum.....	1
Ulcerative colitis.....	1
Diverticulosis colon.....	5
Atonic right colon.....	14
Atonic whole colon.....	22
Marked redundancy colon.....	30
Spastic left colon.....	7
Marked general visceroptosis.....	2
No abnormality.....	22

To summarize the gastro-intestinal findings, the most outstanding abnormality was deficient gastric acidity in seventy patients and colon disease in sixty-six; sixty of the latter showed some degree of atony or marked redundancy. In the whole group of 100 cases only three patients were entirely free from gastric symptoms, abnormal roentgenographic findings or disturbance of the gastric secretion. All others showed definite change from normal in one or all of these ways.

What significance do these findings in the gastro-intestinal tract have in relation to arthritis? Could they be merely changes that result from a disturbed general nutrition, secondary to the arthritic process? Haft<sup>6</sup> compared two series of twenty-five cases.

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One group of patients had arthritis and the other had some wasting disease, and the findings in the colon were essentially the same. He believed the colon changes were only the result of disturbed nutrition. My experience does not entirely confirm these findings.

Are the gastro-intestinal symptoms in arthritis of no significance whatever? A moderate, although definitely smaller proportion of patients whose only complaint is mild digestive disturbance, also exhibit the same findings and their nutrition is not even always impaired. It is possible that these patients are potentially arthritics, but lack some other factor to produce the disease.

For the present, I think both these possibilities should be dismissed, because, in a disease so devastating to human happiness and economy, one should keep an open mind about any abnormality frequently found in association with the disease. It is well to recall how long it took to solve the riddle of achlorhydria and pernicious anemia. One thing that has impressed me, as a possible indication that the gastro-intestinal tract may be involved prior to the onset of arthritis, is that so many of the patients very early in the course of arthritis showed distinct changes, both in the gastric acidity and lack of tone of the colon. If these changes are primary and not secondary to wasting disease, is it amiss to speculate about what causes them? Changes in gastric acidity and in the tone of the colon are frequently associated with various types of deficiency disease, pernicious anemia, sprue, pellagra, iron deficiency anemia, etc. Deficiency of some as yet unknown substance as a factor in arthritis certainly possesses attractive theoretical possibilities.

The great majority of arthritic patients have evidence of imbalance of the sympathetic nervous system. Visceroptosis and an asthenic digestive tract, with subacidity, are extremely prevalent in the sympathicotonic individual. Add additional factors, and could the sympathetic nervous system be the underlying factor in chronic arthritis? Adson at the Mayo Clinic already has demonstrated the benefits of surgery of the sympathetic system in selected cases. If we combine these two theories a possible explanation is that heredity, illnesses and feeding difficulties in childhood, overwork and emotional strain, etc., have slowly produced these changes in the sympathetic nervous system and gastro-intestinal tract which result in a chronic lowered nutrition on which the arthritic process is easily grafted.

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From the more practical viewpoint of treatment of chronic rheumatoid arthritis, the gastro-intestinal tract should be considered seriously as a possible factor in the etiology of the disturbed nutrition which almost invariably accompanies the disease. It is only one factor. It should not be regarded as the sole cause, to the exclusion of many other therapeutic approaches. It appears from my experience that patients whose treatment includes some attention to the digestive tract, show a better response than when this is neglected.

Treatment of the gastro-intestinal tract should aim at improvement of the general nutrition, by correcting deficiency of diet and supplying ample caloric, vitamin and mineral intake; by correcting digestive symptoms which interfere with adequate intake; by treatment of the sympathetic nervous system as it applies to the digestive tract; by securing elimination in a natural way; by physiotherapeutic measures to tone up the atonic condition; and when indicated, by replacement of deficient gastric secretion. I am not thoroughly in accord with the opinion that the much advocated low carbohydrate diet should always be used. In some patients this diet aggravates digestive symptoms, and in the extremely malnourished patient carbohydrates can supply a large caloric intake in an easily assimilable form. In such cases the caloric intake is of the utmost importance. I prefer to add carbohydrate in the form of dextrins and sugars, rather than as starches, and to use small doses of insulin which often causes a great increase in appetite with a resultant gain in weight.

In general, I prefer the use of a well-balanced diet, with plenty of protein, calcium and iron. Because it is my belief that some deficiency is a factor in arthritis, and as this deficiency is at present unknown, I feel that calcium and iron and all the vitamins, especially B and D, should also be added in concentrated form and in large amounts. Poor absorption by the gastro-intestinal tract is a logical explanation of the deficiency and large amounts are needed for adequate absorption.

Digestive symptoms must be treated symptomatically. Those commonly complained of are anorexia, gas and distress shortly after eating, bloating, belching, flatus and disturbances of or around the heart from gas pressure. These are best combated by complete rest in bed when possible, or rest after meals, and by decreasing the size and increasing the number of meals. Dilute hydrochloric acid in large doses during and after the meal and nux vomica and gentian before the meal often solve the whole problem of the digestive disturbances. Light wines have a re-



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markably stimulating effect on the appetite. The depressing action of tobacco should be entirely avoided. The sedative effect of bromide and pheno-barbital cannot be dispensed with in many of these nervous patients.

The correction of the disturbances in the sympathetic nervous system is best approached through the emotions. Relieving fears, anxieties and trying to change the patient's mentally depressed state into a state of happiness and contentment, largely through establishing confidence and by a peaceful environment, are among the greatest assets in treatment of the faulty nutritional state.

Bowel management is by far the most difficult problem and one which must be solved, if good results are to be obtained. If it is true that colon stasis does disturb body functions through absorption of toxic substances, then surely the irritation of the bowel with catharsis, irrigations and enemas must result in increased absorption. The difference in the sense of well-being of any patient who gets natural bowel movements confirms this fact, when compared to the way he feels when elimination is secured by unnatural means. Laxatives and enemas which most patients have used for years must, therefore, be proscribed. Here the patient usually offers considerable resistance, and insists that it is hopeless for him to secure elimination except by catharsis and that any effort to do so will only cause great discomfort. It is wise to hospitalize such objectors at the very beginning, in order to be sure that orders are carried out. Otherwise, efforts by the patient are half-hearted and the results are poor, and there is usually an immediate return to the old regimen, which thus becomes more deeply entrenched. Good results restore confidence and many a fight is won or lost on this point. Here again objections can be raised to the strict adherence to the low carbohydrate diet. This diet must of necessity contain considerable roughage, and the asthenic state of the digestive tract will not tolerate such a diet at the beginning of treatment. As the tone of the intestine improves and the irritation resulting from laxatives disappears, then the amount of bulk in the diet can be increased. I prefer to have the patient begin taking a low residue diet, which is better tolerated, encourages him to eat and usually leaves sufficient residue for bowel action. It is better to add non-irritating bulk, such as agar or psyllium seeds, in order to be sure to get results. The occasional tendency to stasis and packing in the cecum is overcome, if these are taken along with plain mineral oil. The patient must be educated to expect no results for at least three days on this routine. Not infrequently good results are obtained on the



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second day. A regular habit time, once daily, is insisted on, and this should be after the morning meal. To encourage this, a fairly large amount of hot liquid and a good breakfast are given. This is followed by exercise or abdominal massage for fifteen minutes and then if no desire for defecation occurs, a glycerine suppository is used. Obstinate constipation requires additional procedures, such as oil injections into the rectum at bedtime and Morse sine wave therapy to the colon. All of these measures are discontinued gradually as results warrant it. I want to emphasize here the importance of the good results obtained with gentle abdominal massage. The chiropractors and osteopaths capitalize very strongly on this simple method. I have no objection to the occasional laxative or enema, which I think is beneficial in many instances, and the old custom of a routine monthly dose of calomel and saline possesses many virtues, but one must be sure if these measures are used that they do not cause the patient to return to the old faulty habits. Large doses of vitamin B in any potent form are a very valuable aid and apparently possess some power to increase tone in the colon. The spastic type of constipation is so rare that the use of belladonna seldom is required. In addition to massage, the chief physiotherapeutic aid to the function of gastro-intestinal tract is postural exercises, and especially deep breathing exercises. In the severe cases these must be very mild at first, but should never be neglected, as they apparently are a great stimulus to metabolism, which is usually quite low and usually does not respond to thyroid medication.

Recent work, especially by Bloomfield and Polland,<sup>7</sup> seems to cast some doubt on the significance of subacidity and achlorhydria. These patients usually tolerate dilute hydrochloric acid very well and I feel that its administration adds just one more factor to the securing of a better nutritional state. It should be given in doses as large as can be tolerated.

With this treatment, in addition to the other measures routinely used in the treatment of rheumatoid arthritis, the improvement in the nutritional state has generally been good, with concomitant improvement in the function and decrease of pain in the joints. In the cases in this series in which it was possible to get follow-up roentgenologic studies on the colon, the improved tone was easily demonstrable.

The significance of these findings and the value of treatment might be very seriously questioned by any hypercritical observer or the therapeutic nihilist. But results with any type of treatment in rheumatoid arthritis are far from satisfactory, so any

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addition to the therapeutic regimen that offers the slightest encouragement should certainly be given a fair trial in this discouraging disease.

There is one more point, and I think a very important one, to make about these findings in the gastro-intestinal tract. If, by chance, subacidity and an atonic colon are found in a non-arthritis patient, might not a certain proportion of patients be saved from arthritis by early institution of a more rigid treatment than might be advised otherwise if these findings were disregarded as having no possible relation to joint disease. To try to substantiate this, very recently I have been studying the sedimentation rate on such patients who do not have arthritis. While the series is still very small, the rates are as high, in many cases, as in patients with arthritis, which I feel may be of very definite significance in relation to the whole problem.

In conclusion a plea has been made and some suggestions have been presented for improving the general nutritional state of the rheumatoid arthritis or potential arthritis patient by careful attention to the findings in the gastro-intestinal tract.

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## SARCOMA OF THE STOMACH

### Report of a Case

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Sarcoma of the stomach is a rare lesion which comprises from 1 to 2 per cent of all gastric neoplasms and which may cause considerable difficulty in diagnosis. The clinical evidence may suggest the presence of carcinoma, but the roentgenologist may find no evidence of neoplasm. In dealing with an obscure diagnostic problem, a consideration of the rare possibility of sarcoma and its different pathologic process from that found in carcinoma, may result in earlier diagnoses and explorations. The operability and curability of sarcoma appear to be greater than is the case with carcinoma. Jones and Carmody<sup>1</sup> of this Clinic reported a case in which the patient is entirely well nineteen years after gastric resection. Roentgen therapy has proved effective in certain types of this lesion.

The following case wherein total gastrectomy was performed emphasizes the difficulties encountered in making a correct diagnosis of sarcoma of the stomach.

A man, 55 years of age, was first seen on March 5, 1935. His chief complaints were pain in the epigastrium and loss of 20 pounds in four months. A cholecystectomy had been performed four years before. The illness for which he sought relief started five months before he was seen here, with localized epigastric pain which was dull in character and which came on immediately after eating. Roentgen examination which was made elsewhere revealed an ulcer on the lesser curvature of the stomach. Operation had been advised but was refused. The patient was then given daily 24 intramuscular injections of 4 per cent solution of 1-histidine monohydrochloride (trade name — LaRostidin), which gave relief from symptoms until 4 weeks before our examination. The pain then recurred and became practically constant. It was made worse by food and often wakened the patient at 4 a.m. There was no vomiting. Another series of injections of LaRostidin gave no relief.

When the patient came here, abdominal examination revealed a large incisional hernia medial to the upper right rectus scar from the cholecystectomy. There were no palpable masses. Blood examination gave the following findings: red cells 4,680,000, hemoglobin 97 per cent, white cells 5,200. Otherwise the examination was without significance.

On the night following the examination, a gastric hemorrhage occurred at 2 a.m. The patient entered the hospital the following morning and was placed on strict management. At the time of the roentgen examination, ten days later, care was taken to avoid any palpatory manipulation under the fluoroscope. Under these circumstances, the duodenal bulb was not well visualized (high steerhorn type of stomach) and there was an apparent deformity which was believed to be due to a duodenal ulcer. The stomach showed no evidence of abnormality.

Symptomatic improvement occurred for a time, but later while the patient was on strict ulcer management, the epigastric discomfort returned and included night distress at 2 a.m. The test meal revealed an absence of free hydrochloric acid and the ben-zidine reaction for blood was positive.

A progress roentgen examination of the stomach made approximately three weeks after the patient entered the hospital would have revealed normal findings had not a careful study of the gastric rugæ been made. A study of the gastric rugæ after the ingestion of a small amount of barium revealed an irregular ulceration on the posterior wall and lesser curvature which suggested a neoplastic process.

At operation, a large gastric ulcer was found which involved the posterior wall of the stomach and extended well up into the cardia. Because of the extent of the induration and infiltration associated with the ulcer, the lesion was considered to be carcinomatous. There was no widespread glandular involvement, so Dr. T. E. Jones performed a total gastrectomy.

A pathological study of the entire stomach revealed an indurated mass on the posterior wall of the stomach just below the lesser curvature. On opening the stomach, a large indurated ulcer was found which measured 9 cm. longitudinally and 7.5 cm. transversely and extended from the cardiac opening toward the pylorus. It was situated in the posterior wall but extended to the lesser curvature and anterior wall. The distal margin of the ulcer was 6 cm. from the pylorus. Microscopical study revealed a diffusely infiltrating lymphosarcomatous growth which involved all the coats of the stomach. Sections of three lymph nodes from the lesser omentum showed no evidence of metastasis.

#### DISCUSSION

Our experience has shown that when roentgen examination reveals evidence of a gastric ulcer and operation is not performed, the most important criteria relative to the question of carcinomatous involvement are the progress roentgen examinations. If

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an ulcerating carcinoma is present, an increasing deformity characteristic of carcinoma will be seen even though symptomatic relief may be obtained by the so-called medical "therapeutic test." Cases which by exploration have been determined inoperable carcinomata have had complete relief from symptoms and a restoration of the blood count to normal for many months by the use of the appropriate medical management. On the other hand, if the gastric ulcer is benign, unless there are clear-cut indications for surgical treatment, the progress roentgen examinations will show a marked diminution or complete disappearance of the deformity along with the relief from symptoms, while the patient is following a medical regimen for the management of ulcer.

This case is reported for the purpose of warning against the infallibility of the progress roentgen examination in the case of sarcoma, because of the different pathologic process encountered here as compared with that of carcinoma. This case also illustrates the relief from symptoms which may be secured by medical management in the presence of neoplasm.

In the presence of sarcoma of the stomach, the gross pathologic changes may be limited to a thickening of the stomach wall without any involvement of the mucosa. If a palpable mass is present, the roentgenologist may believe it has no connection with the stomach. The gastric lumen is seldom encroached upon.

The extra-gastric variety which is most common and which arises from the subserous connective tissue layer of the stomach, usually spreads between the layers of the gastro-hepatic or gastro-colic omentum, and may involve very little of the stomach wall. The mass usually arises from the posterior surface or the greater curvature and obstruction is a rare finding.

The variety which arises in the submucosa spreads under and lifts the mucosa, involving a variable degree of the stomach. Finally it projects either into the lumen of the stomach or out under the peritoneum, more often the latter.

The third, or infiltrating variety, usually like linitis plastica, involves a large part of the stomach.

The *age incidence* has been reported by some authors to be from five to twenty years below that of carcinoma. The patient reported by Jones and Carmody was 10 years of age, but in all the collected cases, the greatest prevalence has been in the fifth decade of life.

The *symptoms and signs* of a localized sarcoma of the stomach are, of course, similar to those of carcinoma, except for an occa-

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sional case in which the duration of symptoms is longer — often as long as a year or more before the surgeon sees the patient.

From the standpoint of *treatment* the reported cases show a higher percentage of operability and curability than do those of carcinoma of the stomach. Roentgen therapy has proved valuable in cases of localized lymphosarcoma.

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## MALIGNANT DISEASES OF THE THYROID GLAND \*

U. V. PORTMANN, M.D.

Within recent years better understanding of malignant disease has brought the realization that the histologic morphology of the tissue is not always a criterion by which such growths may be differentiated or classified, and does not always indicate what may be their clinical course. This is particularly true of the malignant tumors of the thyroid gland, there being certain points in their origin, development, structure and growth characteristics which are just as important as their microscopic morphology and must be taken into consideration in order to distinguish the different types of growth and to understand the reasons for their peculiar variations. Therapeutic procedures should be planned on the basis of the growth characteristics of each different type of neoplasm.

### DEVELOPMENT AND STRUCTURE

The main body of the thyroid gland originates from an anlage in the primitive pharynx as an outgrowth of epithelial cells on its dorsal surface. Two lateral anlages also appear but are unimportant except as they may become aberrant thyroids. The anlage of the thyroid enlarges by progressive hyperplasia of the epithelial cells into a glandular arrangement to form the individually peculiar terminal compartments, or acini, which constitute the functioning part of the gland. No excretory ducts are formed. From the mesothelial bed of the primitive thyroid a fibro-elastic capsule and stroma develop to form septa which divide and subdivide the organ into lobes, lobules and a large number of terminal acinar vesicles. The glandular epithelium of the acini lies directly upon the connective tissue stroma, there being no true basement membrane.

The concentric hyperplastic development of the glandular structures of the thyroid causes the oldest cells to lie in the center of the lobules and therefore not infrequently a superfluity of closely packed cells may be amassed within certain lobules, thus forming a nodule or tumor composed of modified glandular structures, and this is an adenoma. Because of their embryonic character the adenomas of the thyroid, as is true of similar tumors in glandular organs, may undergo many changes of function, growth or degeneration.

The thyroid gland is abundantly supplied with blood vessels. The large bilateral superior thyroid arteries to the lateral lobes

\*Reprinted by permission from American Journal of Roentgenology and Radium Therapy, 32:508-515, October 1934.

are branches of the external carotids, and the paired inferior arteries come from the subclavians. These vessels terminate as a rich plexus of arterioles and capillaries within the connective tissue which surrounds the acini so that the epithelial cells are separated from the circulating blood only by the thin endothelial lining of the vessels. Veins and venous sinuses also are very numerous in the gland, and empty into a large plexus beneath the thyroid capsule from which the blood escapes into the thyroid veins. The bilateral superior and middle veins empty directly into the internal jugulars and the inferior veins which drain the deeper parts of the gland empty into the left innominate vein. Thus the venous communication is directly to the superior vena cava and thence to the heart.

The lymphatic vessels follow the course of the blood vessels, most of the main stems passing to the superior deep cervical lymph nodes. The lymph vessels of the isthmus and adjacent parts of the lateral lobes also drain to the anterior surface of the trachea and there is a direct communication from the capsular lymphatic plexus to the neighboring structures.

#### CLINICAL ASPECTS OF DEVELOPMENT AND STRUCTURES

This review of the development and anatomic structure of the thyroid is important from the clinical standpoint for the following reasons, which will be discussed later in connection with the different types of malignant tumors.

(1) Thyroid tissue consists largely of glandular epithelial cells. Hence, on the basis of the laws of probability, epithelial neoplasms or carcinomas should occur with proportionately greater frequency than the mesothelial neoplasms or sarcomas.

(2) The character of the concentric and hyperplastic development of the thyroid glandular structure predisposes to the production of localized adenomatous tumors which may undergo many kinds of degenerative changes, including malignancy, because of their inherent embryonic stimulus to hyperplastic growth.

(3) The acini of the thyroid have no basement membrane, and because their cells lie in such close proximity to the vessels, they may readily penetrate into the circulating blood and may be quickly distributed to different parts of the body as metastases.

(4) The lymphatic distribution and drainage of the thyroid cause the deeper cervical lymph nodes to be involved by certain types of malignant processes fairly early, frequently before they

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can be determined clinically, and the abundant infracapsular plexus permits direct extension to adjacent structures, particularly to the trachea.

### MALIGNANT ADENOMAS

The term malignant adenoma was suggested by Dr. Allen Graham to designate those carcinomas of the thyroid which originate in pre-existing adenomas, exclusive of the papillary cyst adenomas. This group constitutes about 90 per cent of all malignant lesions of the gland, and at least 90 per cent of the epithelial thyroid malignancies can be proved to have originated in pre-existing adenomas.

When a pre-existing benign adenoma of the thyroid undergoes malignant change, the growth may present many combinations of morphologic transitions such as fetal, intermediate or mixed colloid adenomas, and any one, two or all of these transitions may be found in a single tumor; in fact, it is seldom that only one type is found. Therefore, adenocarcinoma, medullary carcinoma, scirrhous carcinoma, papillary carcinoma or carcinoma resembling sarcoma or any combination of these forms may occur in a malignant adenoma, or may be found in thrombi within the vessels. Because of this variability of structure, it is difficult to make a diagnosis of the type of growth on the basis of morphology alone; therefore, before the true character of the neoplasm can be established it is necessary to study the type of structure of the pre-existing adenoma, its duration and rate of growth, the character and reaction of the stroma, and especially the evidence of invasion of the blood vessels.

The difficulty which attends the diagnosis of these neoplasms and the chance of making an error, if only the histologic morphology of the tissue is taken into consideration to the exclusion of the other characteristics, is illustrated by the following reviews. Over a period of about twenty years, up to 1932, there were 330 cases at the Cleveland Clinic which were thought to be malignant thyroid neoplasms. Of these, 186 were diagnosed as malignant adenomas because of their histologic morphology by four or five different pathologists. When they were reviewed a few years ago by Dr. Allen Graham it was necessary to discard 108 cases as not malignant, leaving only 78 cases of true malignant adenoma. As shown by Table 1, this elimination of so many cases was probably correct because of the 108 cases eliminated, only 4 patients are dead and all from some intercurrent disease, while of the 78 patients finally proved to have malignant adenoma, 46 are dead of malignant disease. Treatment evidently was not a factor in the low mortality in the group of cases dis-

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TABLE I  
MALIGNANT THYROIDS  
*Series of Cleveland Clinic Foundation to 1931*

	Total	Traced	Living	Dead	Dead Per cent
No operation.....	48	36	5	31	86
Operation—no pathology.....	15	10	1	9	90
Parastruma.....	1	1	0	1	100
Epidermoid.....	1	1	0	1	100
Myxosarcoma.....	1	1	0	1	100
Lymphosarcoma.....	11	10	2	8	80
Spindle cell.....	5	4	1	3	75
Sarcoma-carcinoma.....	5	5	1	4	80
Carcinoma—unclassified.....	16	15	2	13	87
Scirrhus.....	6	6	0	6	100
Papillary.....	15	15	9	6	40
Malignant adenoma.....	78	71	25	46	65
Adenocarcinoma not in adenoma.....	17	16	16	0	0
Multiple types.....	3	3	3	0	0
	222	194	65	129	
Adenomas discarded by Dr. Graham.....	108	86	82	4	

carded, because but few of these patients were irradiated, while the 78 patients with true malignant adenoma had both operation and irradiation in most instances.

This discussion illustrates the error which may be made in considering a thyroid tumor to be malignant when it is not malignant if only morphology of the tissue is the criterion on which the diagnosis is made.

An error in the opposite direction is illustrated by the statement of Wilson\* who said:

"In the Mayo Clinic, of ninety-seven patients operated on who have died of the disease or who when last heard from were known to have undoubted recurrences, usually metastatic, there were fifty whose clinical histories before the first operation contained no suggestion of malignancy. The glands removed at operation from all of the ninety-seven were examined pathologically, yet at the first operation twenty-three of these were passed by the pathologist without suspicion of malignancy."

This quotation suggests that a considerable number of malignant thyroid growths may escape the observation of the pathologist if only the morphology of tissue is the basis for the diagnosis.

\* Wilson, L. B. Malignant tumors of thyroid. *Ann. Surg.*, 1921, 74, 129.

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Of course, these errors were made in a period years past and since that time the accuracy of diagnosis has improved considerably, but there still exists the possibility of error in either direction.

Malignant adenomas are primarily encapsulated by the connective tissue which surrounds the pre-existing adenoma, but since the neoplastic epithelial cells lie in direct contact with numerous blood vessels in and around the tumor, these will be filled with neoplastic cells in almost every instance by the gradual expansion and invasion of the growth. They metastasize by way of the blood stream even though the growth may not have broken through its own capsule. This manifestation in the blood vessels is characteristic and distinguishes malignant adenomas no matter what the histologic structure may be.

Malignant adenomas are found in patients past middle age who have had a goiter for a long time which has begun to enlarge suddenly. The progress of the enlargement may be relatively slow, even with occasional regressions unrelated to any physiologic process. A hard tumor is found in the thyroid, usually unilaterally, but a smooth, firm, general enlargement sometimes occurs depending somewhat upon the duration and the rate of growth.

About half of the cases can be diagnosed clinically, the others being discovered by the pathologist after removal of thyroid tissue for goiters, supposedly benign.

### ADENOCARCINOMA NOT IN ADENOMA

Occasionally a peculiar lesion is encountered in the thyroid which may be called "adenocarcinoma not originating in adenoma." This lesion has some characteristics of carcinoma but is of very low grade malignancy. It originates in acinar epithelium, remains quite localized, is not encapsulated and no mitotic figures are demonstrable. It might be called "carcinomatoid" and is only of interest to pathologists, as it gives no clinical signs or symptoms and is not fatal.

### SCIRRHUS CARCINOMA

The sort of stimulus to neoplastic growth which causes a scirrhous carcinoma to develop in the thyroid gland produces the same histologic changes in this organ as are found in scirrhous carcinomas in other structures. Fibrous tissue predominates and the neoplastic epithelial cells occur in masses of strands as if the malignant reaction were held in restraint so that glandular arrangement cannot take place. The growths are not encapsulated and, therefore, progressively invade the surrounding tissues

which they destroy by infiltration through the lymphatics and compress the blood vessels in fibrous tissue. It cannot be determined that scirrhus carcinomas of the thyroid begin in adenomas, though there is no reason why they should not do so. As previously mentioned, a malignant adenoma may present localized areas of scirrhus formation along with other types of malignant changes.

These neoplasms seldom are discovered early by clinical examination but in the late stages and after recurrence, they are extremely hard and fixed and the invaded lymph nodes are sometimes palpably enlarged. They grow very slowly but progressively and are of low grade malignancy from the standpoint of rapidity of growth but destroy life by local constriction even before metastases develop.

#### PAPILLARY CARCINOMAS

Adenomas of the thyroid, like adenomas in other organs, may also undergo cystic degeneration and in turn these cystic adenomas may become malignant. When this occurs, multiple finger-like processes are formed in the walls of the acini in the arrangement which is characteristic of papillary carcinoma. The growth is at first confined within its capsule, but gradually the neoplastic columnar cells of the papillæ invade and break through the thin stroma at the base of the acini in which they develop, and thus extend to adjacent acini and the lymphatics. They do not invade blood vessels, because of the avascularity of the cysts in which they originate, and because they are confined and primarily encapsulated. As would be expected from the nature of their origin and the character of their growth, these neoplasms are of a comparatively low grade of malignancy. As indicated previously, some malignant adenomas may contain areas with papilliferous formation.

Clinically, the papillary carcinomas are usually unilateral, rather firm, nodular tumors which grow slowly but sometimes become very large. As the tumor progresses the structures about it are infiltrated and compressed and the skin may become red and edematous with eventual breakdown and ulceration.

#### CARCINOMA-SARCOMA

A rare tumor of mixed carcinoma and sarcoma occurs in the thyroid. The epithelial structures show changes characteristic of carcinoma and the abundant stroma presents the appearance of fibrosarcoma. There are numerous mitotic cells arranged atypically in both epithelial and mesothelial elements. Theoretically, this type of tumor may begin as carcinoma which, because of some



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peculiarity of growth or physiologic reaction, causes neoplastic stimulus to the stroma so that it also becomes malignant. However, there is little proof of the theory. Usually this tumor is erroneously considered to be carcinoma, or is occasionally classified as fibrosarcoma, depending upon the type of cells which are found. There is no possibility of differentiating this growth clinically; it must be distinguished by microscopic examination. It appears as a hard, rapidly extending mass in a lobe of the thyroid.

### SARCOMA

True sarcomas of the thyroid are rare in spite of the fact that the literature contains many reports of such cases. If the relative proportion of mesothelial elements to the epithelial structures is taken into consideration, it must be realized that sarcomas should be comparatively uncommon. The usual mistake is to call a very cellular, malignant adenoma a sarcoma. However, sarcomas originate in the mesoblastic elements of the stroma and a study of different regions will usually distinguish them from malignant adenomas by the absence of epithelial cells in the tumor.

The most common type of sarcoma of the thyroid is lymphosarcoma and it has the same characteristics as similar neoplasms in any other organ. The growth is highly malignant and quickly infiltrates the thyroid and adjacent structures. Clinically, patients with lymphosarcoma give a short history of very rapid growth and usually the entire organ is firm and fixed and the patient complains bitterly of choking. The rapid infiltration of the gland and adjacent structures, particularly extension into the upper mediastinum, usually destroys the host before distant metastases become evident.

Fibrosarcomas, or spindle cell sarcomas, originating in the stroma also are seen occasionally, but they are very rare. They grow more slowly than lymphosarcomas and clinically are indistinguishable from other tumors.

### METASTASES

Every patient for whom an operation on the thyroid is contemplated should first have a roentgenographic examination of the chest. Such an examination may reveal unsuspected benign intrathoracic or substernal thyroids or metastases from a malignant goiter that may or may not be discovered by clinical examination. Pulmonary metastases usually are seen as multiple tumors or as a shower of small nodules of various sizes, particu-

larly in the bases and they gradually enlarge and coalesce as the disease progresses.

Metastases may also occur in bones, especially in long bones, but also to some extent throughout the rest of the skeletal system. When an otherwise unexplainable, but obviously malignant, lesion is discovered in a bone by roentgen examination, the thyroid should be suspected as the primary source of a neoplasm, even though there may be no other evidence of disease of this organ.

Occasionally metastases occur in soft tissues as slowly growing tumors without any definite clinical characteristics and only microscopic examination will disclose their thyroid origin.

Distant metastases are almost always from malignant adenomas. They develop from neoplastic cells which have invaded blood vessels, become detached and are distributed through the circulation and form neoplastic emboli in various locations. The other types do not often produce distant metastases because these growths extend through the lymphatics. Because metastases have the histologic morphology and probable function of the parent neoplasm which may closely resemble normal thyroid tissue, they have been mistaken for aberrant thyroid rests.

When metastases are present, operations upon the thyroid usually are not indicated. However, even when metastases are present or when the growth has invaded the structure contiguous to the thyroid, it may be necessary to do a decompression operation to remove some of the growth, or to perform a tracheotomy in order to relieve respiratory difficulty. Roentgen irradiation should be administered following such palliative operations to inoperable neoplasms and to metastases, some of which may thus be held in check for some time.

#### TREATMENT OF MALIGNANT GOITRE AND ITS RESULTS

The procedure for the treatment of malignant tumor of the thyroid should be based upon its known growth characteristics. Only about 50 per cent of cases can be diagnosed clinically before operation; therefore, half of them have had some sort of operation and are only discovered by the pathologist.

When a definite diagnosis of malignant goiter can be made by clinical examination the condition usually is inoperable from the standpoint of curability because of the probability of invasion of the vessels in the tissues which cannot be removed. Sometimes, however, palliative operations are advisable and at least a biopsy should be done to determine the type of neoplasm in order to

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carry out a logical therapeutic procedure. In any case, in operating on a patient with malignancy of the thyroid, the surgeon should always have in mind the possibility of causing embolic metastases by harsh manipulation.

In our series of 48 cases of different types of malignant disease of the thyroid which were considered to be inoperable, 36 patients have been traced and 5 are still alive; the longest survival in a proved case has been ten years. This patient received roentgen irradiation following a postoperative recurrence of a malignant adenoma. The average length of life of the patients living has been forty-one months and of the dead was twenty-seven months.

When a malignant adenoma is discovered, treatment is begun with roentgen irradiation regardless of whether or not the surgeon believes he has removed all of the growth, because there is always the possibility of invasion of the blood vessels outside the field of operation. Since about 90 per cent of the malignant neoplasms of the thyroid are malignant adenomas, the blood vessels are probably invaded and so interstitial irradiation is seldom employed at the time of operation. This treatment may be used with less hazard after the neoplasm has been rendered dormant by roentgen irradiation, or later, if it is obvious that the roentgen treatment has not been entirely efficacious. Most of the malignant adenomas are quite sensitive to irradiation not only because the neoplastic cells in the tumor and those in the vessels are radiosensitive, but also, no doubt, because of the secondary fibrosing and obliterating effect upon the capillaries which prohibits further extension. Roentgen irradiation alone has been quite efficacious in our experience.

Of 78 cases of proved malignant adenoma in our series, 32 per cent of the patients are alive, the longest for seventeen years and the average for six and one-fourth years.

The *adenocarcinomas not originating in adenomas* are so localized and of such low grade malignancy that none of them require irradiation. Of 17 patients with this carcinomatoid growth, 16 of whom have been traced, all are well.

Scirrhus carcinomas may be recognized at operation as a very hard growth. It is almost a certainty that such a growth has invaded the lymphatics and other structures contiguous to the thyroid and has extended widely through the lymphatics, and for this reason cannot be entirely excised. Scirrhus carcinomata are highly resistant to irradiation, and since they destroy life before distant metastases develop, they should have interstitial irradiation followed by roentgen irradiation, although even with

this procedure the prognosis is very bad. Of the 6 patients we have seen, all of them are dead; the patient who survived for the longest period after operation lived for only six months.

Occasionally a papillary carcinoma may be so localized and encapsulated that it may be excised completely, but when there is clinical, gross or microscopic evidence or a suspicion that the growth has extended through the lymphatics into the surrounding thyroid gland structure or adjacent tissues outside the field of operation, irradiation should be administered. These growths do not invade blood vessels early as do malignant adenomas, and therefore the application of interstitial irradiation is not so hazardous. If and when this type of growth is recognized at operation, interstitial irradiation may be applied at once to be followed later by roentgen treatment. If the neoplasm is discovered subsequent to operation, it is advisable to depend upon roentgen irradiation unless growth continues, and then a second more extensive operation and implantation of radium in one form or another may be necessary. Some of these growths yield to irradiation. Papillary carcinoma has been found in 15 of our cases. Nine patients are alive, one ten and three-fourths years and the average for six years.

The carcinoma-sarcomas and the spindle cell sarcomas are also highly malignant and radioresistant, and usually only recognizable by the pathologist. Of 5 cases of carcinoma-sarcoma at the Cleveland Clinic, the longest survival period was eleven months and all 5 patients with spindle cell sarcoma died within five months.

The lymphosarcomas of the thyroid are more undifferentiated and therefore more radiosensitive. Operation alone seldom can effect a cure and it is advisable to employ both interstitial and roentgen irradiation. Eleven lymphosarcomas have been encountered in our series; 9 of the patients were traced, 1 died immediately postoperatively and of the 7 known dead, the longest survival period was seven months. One patient is still alive after ten years and another has been well for almost two years; these patients had roentgen therapy following operation.

#### TECHNIQUE OF IRRADIATION

The technique of applying radium irradiation to malignant goiters should be planned according to the type and size of growth. The more resistant neoplasms should be given as great an intensity as is possible. Either gold radon seeds or needles may be employed as indicated, the former preferably for the infiltrating growths and the latter for those larger tumors. The

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container should be placed to irradiate the trachea without damaging it. As has been pointed out, it is better not to thrust needles into malignant adenomatous tissue, and so roentgen irradiation should be employed primarily to be followed by interstitial irradiation, if necessary.

In administering roentgen irradiation we have been using 200 kv. and heavy filtration (0.5 to 0.75 mm. Cu) giving an effective wave length of about  $0.15\text{\AA}$ .

The skin tolerance dose is considered to be 800 roentgens when back-scattering is included.

The fields are planned to crossfire anteriorly and posteriorly the thyroid area, the supraclavicular region and the upper mediastinum regardless of whether or not the growth is considered to be bilateral. The roentgen beam is directed to the midline from each portal and includes the trachea and thyroid isthmus which should receive a therapeutic dose on account of the probability of neoplastic invasion. Inflammation within the trachea may ensue at the height of the irradiation reaction, but usually can be relieved by intratracheal injections of oil, although in some patients who have had extensive invasion necessitating large doses of radiation, a tracheotomy may be necessary. Ulceration in the trachea has been produced in a few instances but this has not been a serious complication and the temporary discomfort is better than death from the disease.

The cases of malignant thyroid neoplasms which have been discussed are from the surgical services of Dr. George W. Crile, Dr. William E. Lower, Dr. Thomas E. Jones, and Dr. Robert S. Dinsmore of the Cleveland Clinic Foundation. All of the cases have been studied pathologically by Dr. Allen Graham. Of the total of 257 proved cases of malignant disease of the thyroid seen before 1932, 222 are included in this report; the others are too recent to be of interest. One hundred and eight additional cases, at first considered to be malignant on the basis of their histologic morphology, have been discarded after more detailed study by Dr. Graham because of insufficient evidence of malignancy. Unfortunately, some of these discarded cases have been included in previous reports.

## GUESTS

On January 25, Dr. Arnold Knapp of New York City was a luncheon guest.

Dr. James L. McLester, President-Elect of the American Medical Association was a guest at luncheon on February 18. Dr. McLester gave a short talk on nutritional diseases.

The Clinical Society of Genito-Urinary Surgeons held their fourteenth annual meeting at the Cleveland Clinic on February 22 and 23.

Dr. Arnold K. Knapp, Health Commissioner of the City of Cleveland addressed the Staff of the Cleveland Clinic at the regular Wednesday evening Staff Meeting on February 27. Dr. Knapp spoke on "The Hygiene of the Community."

On March 15, Dr. Walter Dandy, Professor of Surgery, Johns Hopkins University, Baltimore, was a guest at luncheon and spoke on "Tumors of the Spinal Cord."

The Cleveland Neurological Society held its twentieth regular meeting at the Cleveland Clinic on March 20.

The Industrial Medicine and Orthopedic Section of the Academy of Medicine of Cleveland held its regular meeting at the Cleveland Clinic on April 17.

Dr. Gunnar Nystrom of Uppsala, Sweden, was a luncheon guest on April 19. Dr. Nystrom gave a short talk on "Embolism."

The regular meeting of the Cleveland Radiological Society was held at the Clinic on April 22.

Operative Clinics were held for the Sectional Meetings of the American College of Surgeons on April 25 and 26.



## FRANK E. BUNTS LECTURES

The following lectures have been given under the auspices of the Frank E. Bunts Educational Endowment Fund:

- March 4. Dr. Anton J. Carlson, Frank P. Hixon Professor of Physiology, University of Chicago, "Studies on the Hunger and Thirst Mechanism."
- April 2. Dr. G. V. Anrep, Professor of Physiology, University of Cairo, Cairo, Egypt, "The Coronary Circulation."
- April 29. Dr. Howard Haggard, Associate Professor of Applied Physiology, Yale University, "Medical History and Medical Propaganda."
- May 27. Professor William K. Gregory, Professor of Vertebrate Paleontology, Columbia University, Curator of the Department of Comparative Anatomy and Ichthyology, American Museum of Natural History, "The Rise and Deployment of the Vertebrates with Special Reference to the Origin of Man."

## RECENT PUBLICATIONS BY MEMBERS OF THE STAFF AND FELLOWS

- George Crile and J. E. Kearns, Jr.: Branchial Carcinoma: Lateral Cervical Neoplasms, *Surg. Gynec. Obst.*, 60:703-709, March 1935.
- George Crile: The Energy Background of the Genesis of Gall Stones and of the Prevention of Immediate Postoperative Shock and of Later Digestive Disturbances, *Surg. Gynec. Obst.*, 60:818-825, April 1935.
- George Crile: Newer Methods of Treating Peptic Ulcer, Constipation, and Indigestion, *New York State J. Med.*, 35:422-428, April 15, 1935.
- George Crile: Franklin H. Martin and the American College of Surgeons, *Surg. Gynec. Obst.*, 60:902-904, May 1935.
- George Crile: The Advancing Frontier of Medicine, *The Centaur*, 40:419-421, May 1935.
- W. J. Engel: Urologic Problems in Childhood, *Radiology*, 24:183-192, February 1935.
- A. C. Ernestene: The Mechanism of the Circulatory Changes Accompanying Insulin Hypoglycemia, *Am. J. Physiol.*, 111:440-447, March 1935. (with Riseman, Stern, and Alexander).
- W. J. Gardner and W. B. Hamby: Visualization of Suprasellar Tumors by Encephalography, *Am. J. Roentgenol. & Rad. Therap.*, 33:1-9, January 1935.
- Otto Glasser: The Physical Determination of Radium Dosages, *Am. J. Roentgenol. & Rad. Therap.*, 33:293-295, March 1935.
- Otto Glasser: Induced Ultraviolet Fluorescence and Its Release by Visible Light, *Physical Review*, 47:570, April 1935.
- Russell L. Haden: The Red Blood Cell of Man, *International Clinics*, S. 45, 1:69-92, January 1935.
- Russell L. Haden: Classification and Differential Diagnosis of the Anemias, *J.A.M.A.*, 104:706-710, March 2, 1935.
- Russell L. Haden: A new clinical model of the Haden-Hausser Hemoglobinometer, *J. Lab. & Clin. Med.*, 20:762-765, April 1935.
- Russell L. Haden: The Volume Thickness Index of the Erythrocyte of Man, *J. Lab. & Clin. Med.*, 20:567-571, March 1935.
- W. B. Hamby and W. James Gardner: An Ependymal Cyst in the Quadrigeminal Region, Report of a Case, *Arch. Neurol. & Psychiat.*, 33:391-398, February 1935.
- Charles L. Hartsock: Treatment of the Gastro-Intestinal Tract in Chronic Rheumatoid Arthritis, *Tr. Am. Therapeutic Society*, 34:43-50, 1934.
- C. C. Higgins: Production and Solution of Urinary Calculi, *J.A.M.A.*, 104:1296-1299, April 13, 1935.

RECENT PUBLICATIONS BY MEMBERS OF THE STAFF AND FELLOWS

- C. C. Higgins: Medical Management of Urinary Lithiasis, *Med. Ann. Dist. Col.*, 4:1-4, May 1935.
- Thomas E. Jones: Intestinal Complications Resulting from Prolonged Radium and X-ray Irradiation for Malignant Conditions of the Pelvis, *Tr. Am. Ass. Obst. Gynec. & Abd. Surg.*, 157-164, 1934.
- Thomas E. Jones: The Technique of Abdominoperineal Resection for Carcinoma of the Rectum, *Am. J. Surg.*, 27:194-200, February 1935.
- Thomas E. Jones and Morris G. Carmody: Lymphosarcoma of the Stomach, *Ann. Surg.*, 101:1136-1138, April 1935.
- William E. Lower: The Standard Treatment of Malignant Tumors of the Bladder, *Surg. Gynec. Obst.*, 60:513-515, February 15, 1935.
- William E. Lower: Treatment of Vesicovaginal and Ureterovaginal fistula, *Am. J. Surgery*, 28:234-241, May 1935.
- W. V. Mullin: The Present Status of Infection of the Upper Respiratory Tract in Its Relation to Focal Infection, *New England J. Med.*, 212:50-52, January 1935.
- E. W. Netherton and Bert C. Mulvey: Circumscribed Myxedema, *J.A.M.A.*, 104:1492-1496, April 27, 1935.
- U. V. Portmann: The Treatment of Salivary Fistula by Irradiation, *Ann. Surg.*, 101:1175-1180, May 1935.



## THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

As a memorial to Dr. Frank E. Bunts who for many years was a professor of surgery in the School of Medicine of Western Reserve University and one of the founders of the Cleveland Clinic, the Frank E. Bunts Educational Institute has been endowed by his relatives, friends, and the Cleveland Clinic Foundation. This Institute was chartered on January 7, 1935, by the State of Ohio, to give graduate instruction in all branches of medicine and surgery to those who have graduated from an approved medical school.

The purpose of the Institute is to promote research, to instruct graduate students who now are serving as Fellows in the Cleveland Clinic, to support a series of lectures of both general and medical interest and to sponsor short, intensive, graduate review courses in medicine, surgery, and certain specialties.

The Board of Trustees of the Institute announces the first graduate review course which will be held November 11, 12 and 13, 1935, on "The Diagnosis and Treatment of Diseases of the Glands of Internal Secretion." This course is open to all licensed physicians and surgeons after acceptance of an official application by the registrar. Not more than fifty applications can be accepted. Members of the permanent staff of the Foundation, as well as invited guests specializing in this subject, will conduct the various courses, and the facilities of the entire organization will be available. The fee for the entire course will be \$10.00—five dollars of this is payable on application, and the remaining \$5.00 is payable at registration on Monday, November 11. Application blanks and an outline of the course may be secured from Dr. A. D. Ruedemann, Cleveland Clinic, Cleveland, Ohio.

## DRUG ERUPTIONS

E. W. NETHERTON, M.D.

For practical purposes, the cutaneous manifestations of the toxic effects of drugs may be divided into two groups: (1) Those in which the injury is a result of external contact with the drug; as for example, sulphur, mercury, iodine and other drugs commonly used by the physician, and (2) eruptions which result from the introduction of drugs into the body by various methods, which most frequently is by ingestion. In the first group are classified the cases known as dermatitis venenata. Although individuals vary greatly in their susceptibility to such drugs, their prolonged use, which commonly is by topical applications, produces irritation and if they are used for a long time or in a concentration which is too strong, they will produce dermatitis in a large percentage of patients. The second group is commonly spoken of as dermatitis medicamentosa. In this group there is, likewise, an individual variation in susceptibility. Bromides, iodides, and arsenic when administered for a sufficiently long time will produce an eruption in a large number of patients, while other drugs such as quinine, phenolphthalein, and the various barbituric acid derivatives when ingested by the majority of individuals do not affect the skin, but in a few cases may produce fairly characteristic eruptions. There is a third group of cases in which it has been demonstrated that an eruption develops either after contact or by introduction into the body of a specific drug. Wise and Sulzberger<sup>1</sup> observed a case in which a dermatitis was produced when quinine was applied externally to the skin or when it was taken by mouth. Similar cases have been reported recently by Percival.<sup>2</sup>

The mechanism of the production of drug eruptions is unknown. In the case of contact dermatitis, the epidermis is the seat of the sensitivity and because of this, the patch test as a method of investigation was first employed by J. Jadassohn and has been used in the recent excellent investigations of Sulzberger and Wise.<sup>3</sup> Dermatitis which results from contact with strong irritants which produce traumatic or chemical injury to the epidermis is to be distinguished from cases in which there is an individual susceptibility to a particular drug in concentrations which ordinarily are not harmful to the average person.

Little is known about the mechanism of the production of eruption due to the ingestion of drugs. The seat of tissue susceptibility is yet undetermined. Passive transfer experiments have failed to demonstrate an antigen antibody reaction which occurs in the case of protein sensitization. Intracutaneous injection of test solutions of the suspected drug as well as patch tests have proved to be useless. Therefore, in suspected cases of dermatitis medicamentosa, the physician must



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depend upon the history of the ingestion of a drug, a careful evaluation of the characteristics of the eruption, as well as upon the associated constitutional symptoms. It is important that a proper diagnosis be made in the case of drug eruptions because further administration of an offending drug may in some instances be disastrous. In most instances, the only method of determining that a particular drug is responsible for an eruption is to withhold the suspected agent until the eruption subsides and then to observe the reaction which follows its subsequent ingestion. This is not always practicable or desirable; however, most patients will cooperate with the physician, especially if they have had several attacks.

Practically every active drug has been known to produce an eruption, and as new drugs are introduced, the number of cases of drug eruption becomes more numerous. Almost any type of skin lesion may result from the ingestion of drugs. These range from an erythematous macule to purpura and gangrene and sometimes carbuncular or papillomatous lesions which are produced by iodides and bromides. The eruptions may be generalized and roughly they may simulate exanthemata or they may be limited in distribution and simulate erythema multiforme, late cutaneous syphilis or granulomatous fungus infections. As in the case of arsphenamine dermatitis, the eruption may be an exudative eczematous type of eruption which eventually may terminate as a generalized exfoliative dermatitis which cannot be distinguished solely by its clinical characteristics from an exfoliative dermatitis resulting from other causes.

A single drug may produce a multiformity of lesions, and the eruption may differ in susceptible individuals. For example, phenolphthalein may produce herpes in one person and urticaria or a fixed erythema multiforme like eruption in another. Likewise, similar lesions may be caused by different drugs as in the case of fixed eruption which results from arsphenamine in one case and phenolphthalein or antipyrine in another.

At times, the diagnosis of dermatitis medicamentosa is difficult. In those cases in which the eruption simulates some of the exanthemata, the eruption appears quickly, it usually is more erythematous, and is not associated with the usual signs and symptoms such as coryza, angina, photophobia, koplick spots and fever or prodromal symptoms commonly seen in the various acute infectious diseases. In some instances, when the eruption is acute and generalized, a moderate elevation in temperature may occur. This is especially true in the presence of phenobarbital eruptions which may occur in an individual with acute hyperthyroidism.

When the eruption is of the erythema multiforme type or in instances when the drug eruption simulates some of the better known

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clinical entities, as for example, skin eruptions due to bismuth simulating pityriasis rosea or neurodermatitis,<sup>4</sup> a clinical diagnosis is even more difficult.

An alert physician invariably will give proper consideration to the possibility of dermatitis medicamentosa when considering the differential diagnosis of cases in which the cause is not obvious. This same precaution aptly applies to all cases of dermatitis venenata.

As previously stated, the cutaneous manifestations of the toxic effects of drugs in susceptible individuals vary greatly. Every known elementary dermatological lesion may occur and in some cases there may be a multiformity of lesions. Likewise, no clinical picture is specific for any particular drug. However, certain interesting types of cutaneous lesions result from the introduction into the body of a few of the more commonly used drugs with enough consistency to justify this very brief and incomplete discussion of such a broad subject. I refer particularly to some of the cutaneous lesions which result from the ingestion of bromides, inorganic arsenic, and phenolphthalein. Since these lesions are not particularly common, the profession is not sufficiently familiar with them. These drugs are among those most frequently prescribed by the physician and are also the active ingredients of many proprietary remedies which are used in self-medication.

### BROMIDES

The most common cutaneous manifestation of the ingestion of bromides is an acne-like papulo-pustule which involves the acne areas. The lesions may remain discrete or they may become confluent and form painful, sluggish, indurated pustular patches roughly simulating a carbuncle. The comedo which is the primary lesion of acne vulgaris, is not a characteristic element of this lesion. Years ago, Engman and Mook<sup>5</sup> observed that bromide and iodide eruptions tended to localize around areas of previous inflammation, such as the seborrheic or acne areas. Therefore, it is important to caution individuals who have had severe acne or who are in the adolescent period to abstain from the use of these drugs. Urticaria, vesicular and furuncular lesions may be caused by bromides. A rare nodular bromoderma sometimes occurs on the face and body of infants who are nursing from mothers who are taking bromides, usually for the relief of epilepsy. Bullous lesions may occur, but they are more common in iodide eruptions.

A nodular eruption similar to erythema nodosum occasionally occurs, and this type of bromoderma is not exceedingly rare. I have seen several cases in the past few years, especially in individuals with hyperthyroidism or in neurotic women who have been taking bromides as a sedative. The lesions are cutano-subcutaneous, painful, poorly

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circumscribed nodules which are pink or light red in color. The lesions are not as painful as those of classical erythema nodosum, and they are not associated with acute arthritis or other common manifestations of this disease. In the cases which I have observed, the nodules which resembled erythema nodosum nodules resulting from bromides were true to type in that they did not become softened or break down.

A comparatively rare type of bromoderma is the granulomatous lesion which sometimes erroneously is called a bromide gumma. This lesion occurs more frequently in women, it often follows trauma, and it has a predilection for the pretibial areas or the inner surface of the leg just above the ankle. The eruption may occur as multiple lesions or as a single unilateral, irregular, raised, painful granulomatous plaque varying in size from that of a silver dollar to that of a palm. In some instances, it may involve a large surface of the leg. The margins are raised, doughy, dull red, and sharply defined. The follicles are filled with caseous plugs or a purulent exudate. If poorly cared for, the surface may be crusted or bathed in a very foul pus. Pain and tenderness are outstanding characteristics of this lesion. When the leg is in a dependent position or when the lesion is pressed, the patient experiences great discomfort. Regional adenopathy or lymphangitis does not occur. Late nodular syphilids, gumma, varicose ulcer, blastomycosis, a deeply seated fungus infection, and possibly dermatitis artifacta are the most usual conditions to be differentiated from this type of bromoderma (Fig.1).

Late nodular syphilids are indolent, and nodular or serpiginous, and they tend to ulcerate or disappear spontaneously, leaving atrophic scars which are surrounded by an area of hyperpigmentation. Syphilitic gummata at first are dull red, poorly circumscribed cutaneous subcutaneous nodules which, if untreated, terminate in a deep punched-out ulcer. A varicose ulcer is superficial; it occurs on the lower inner surface of the leg, and is associated with signs of impaired circulation such as edema and varicosity of the superficial veins. If the ulcer has been present very long, a chronic dermatitis or varicose eczema will involve the adjacent skin, and in cases of long standing, the skin becomes sclerotic for some distance around the ulcer. Varicose ulcers frequently are painful, but as a rule they are not as tender as bromide granulomas (Fig. 2).

The similarity between blastomycosis and this type of bromoderma is very slight. Blastomycosis occurs most frequently as an indolent, granulomatous, verrucous plaque on exposed surfaces, such as the face. The pustules which occur near the margin of the lesion are small in comparison with the follicular pustules of bromoderma. Blastomycosis is a chronic condition which spreads, and the plaque may remain unchanged for months or slowly extend at its periphery.



FIGURE 1.—Large granulomatous bromoderma. Note the purulent exudate in the lower portion of the lesion. The outline of the lesion roughly simulates that of late cutaneous syphilis.

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FIGURE 2.—Solitary bromide lesions. The one on the inner surface of the ankle roughly simulates late cutaneous syphilis. This lesion was so painful that the patient was unable to walk without the aid of a crutch. Prompt response was secured after the use of saline therapy.

The diagnosis is established by finding the blastomyces in the material obtained from the small peripheral abscesses.

Other deep-seated fungus infections may simulate roughly the solitary lesion of bromoderma and should at least be considered in the differentiation of this lesion.

Dermatitis artifacta or self-induced lesions, which may occur on the legs of psychopathic or neurotic individuals, are more artificial in appearance, and usually there is a history of previous lesions, some of which may have left scars. Since self-induced lesions result from the application of a chemical or from some mechanical trauma, they more closely simulate contact dermatitis, chemical burns, or traumatic ulcers. Only in the case of an individual who has been shrewd enough to produce a solitary chronic lesion is there apt to be any difficulty in differentiating these two conditions (Fig. 3).



FIGURE 3.—Nodular granulomatous bromide eruption.

Another uncommon bromide eruption consists of papillomatous-condylomatous lesions. The lesions are numerous and bilateral and are found most frequently on the lower parts of the legs, face and arms. The lesions are raised, crusted, papillomatous, dull red, painful plaques or nodules and some have many points of pustulation over their surfaces. The exudate has an offensive odor. These lesions are similar to the larger solitary granulomatous lesion previously described.



## DRUG ERUPTIONS



FIGURE 4.—Pigmented plaques which are the end result of phenolphthalein eruption. This is a good example of recurrent fixed lesions which sometimes are produced by such drugs as phenolphthalein, antipyrine, amidopyrine and arsphenamine.

Bromide eruptions differ from most drug eruptions in that they disappear very slowly after ingestion of the drug has been discontinued. In untreated cases, several weeks may be required before the eruption disappears.

We are indebted to Wile and his associates for the present-day treatment of bromodermas. In 1922, Wile and Wright<sup>6</sup> reported the results of their investigation of eruptions caused by bromide and iodide. Among several important observations, they were able to substantiate the observation of other workers that following ingestion of bromide, a substitution occurred in the body fluids of chloride by bromide. They

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found that the chloride output in the urine increased rapidly after the ingestion of bromide for a time, but eventually gradually returned to normal even though the drug was continued. Because of this, Wile reasoned that it might be possible to displace the accumulated bromides by the administration of large amounts of chloride. In 1923 he<sup>7</sup> reported that three patients who suffered from mental and cutaneous manifestations of bromism were markedly benefited by the intravenous administration of decinormal sodium chloride solution. In these cases, he was able to detect large amounts of bromide in the urine following the intravenous administration of the salt solution. In one of Wile's cases, there was evidence of induced nephritis which resulted from the sudden passage of too large amounts of the bromide salt through the renal epithelium. The frequency of this complication can be decreased by the administration of small initial doses of sodium chloride.

We have had an opportunity to treat several cases of bromoderma by this method and have had exceedingly gratifying results. It has been our custom to start with the intravenous administration of 150 cc. of normal saline solution. Subsequent injections of from 200 to 250 cc. are given every two or three days. The course of treatment usually consists of from three to five injections. After the first injection, the pain and tenderness of the lesion begins to subside. Although large lesions will not disappear completely for several days, the response to this treatment is striking when compared with gradual disappearance of bromide eruptions following the discontinuance of the drug alone.

## PHENOLPHTHALEIN

Another interesting type of dermatitis medicamentosa is the recurring, fixed, pigmentary eruption which is produced by phenolphthalein, antipyrine, amidopyrine, and arsphenamine. This lesion is similar to that seen in erythema multiforme. There may be few or many lesions scattered over the body without predilection for any special region. The lesions vary in size from that of a coin to the size of the palm of the hand. They are roughly oval or round, violaceous to dark red, edematous plaques. The central portion of the lesion is violaceous while the periphery may be light red, depending upon the degree of the inflammatory reaction which is present. In rare instances, the reaction is so intense that bullae form. If the offending drug is withheld, the inflammatory reaction will subside in a few days, leaving a hyperpigmented area. When the drug again is ingested, these pigmented areas become edematous and erythematous as in the preceding attack. This cycle of recurrence and remission of an eruption involving fixed areas is a characteristic of this type of drug eruption. It is important to remember when testing a patient who is

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thought to have a fixed eruption due to phenolphthalein, that it may be necessary to administer more than one dose of the drug, because a recurrence will not always develop with a single dose (Fig. 4).

Abramowitz<sup>8</sup> was the first to prove that phenolphthalein could cause a fixed drug eruption and since his first communication, many cases of fixed eruption caused by this drug have been recorded. Cases have also been reported in which a bluish pigmentation of the nail beds result from ingestion of this drug. Lesions of fixed phenolphthalein eruption, which sometimes involve the genitalia, leave a bluish brown pigmentation which is especially noticeable if the glans penis is involved.

Abramowitz has called attention to the various sources from which an individual may knowingly or unmindfully ingest this drug. It is an ingredient of many cathartic pills and wafers, some of which are extensively advertised by radio broadcasting, and it is used in douche powders. It is found in the coloring used on cake icings. Because of widespread usage it is not surprising that the number of cases of recurrent fixed pigmentary eruption has increased in recent years. The physician should bear in mind that since this drug has been reported to cause urticaria<sup>9</sup> and herpes,<sup>10</sup> it may produce other types of eruptions.

Although the list of drugs which are known to cause fixed eruptions is small, it is to be expected that with the increasing number of new synthetic drugs, the list will be enlarged.

The management of a case of fixed drug eruption is not difficult, provided the offending agent can be discovered. A careful and accurate history is essential. After the eruption has disappeared, suspected drugs should be administered orally until the offending drug has been discovered. It is important to inform the patient of all known sources from which the drug may be introduced into the body. Saline cathartics, forced fluid intake and palliative treatment with calamine lotion with one per cent phenol or some other bland lotion are the only medications that are necessary for the relief of an acute attack.

## ARSENICALS

Another interesting and important condition which results from the introduction into the body of a drug is arsenical keratosis which is produced by the inorganic arsenicals. The common troublesome cutaneous eruptions due to organic arsenicals such as the arsphenamines are an exudative dermatitis, which frequently terminates in an exfoliative dermatitis. Arsenical keratoses should be given special consideration because of their malignant potentialities. The average physician is unaware of the frequent occurrence of these lesions and equally unconcerned in regard to their precancerous nature.

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The palms of the hands and soles of the feet are areas of predilection for arsenical keratoses; however, the trunk and extremities frequently are involved. They develop as hyperkeratotic papules which vary in size from that of a small pinhead to a match head, and they are slightly brownish or skin colored. Their surfaces are cornified. When the lesions are numerous, some areas of the palm may resemble a rasp, and in extreme cases, the palms may show a more or less diffuse keratotic thickening. The patient frequently considers that the lesions are warts. They differ from *verrucae vulgaris* in that they are more uniform in size, are more hyperkeratotic and do not have the papillae or filaments commonly seen in warts.

The lesions on the body and extremities are apt to be larger than those on the hands and feet, and they occur as skin-colored papules with hyperkeratotic apices.

Arsenical keratoses are seen most frequently in individuals who had chorea in childhood and in those who have had psoriasis for many years. These are two common conditions for which inorganic arsenic—Fowler's solution—has, for many years, been considered to be of special value. It is unfortunate that many of our modern textbooks on dermatology continue to advocate the use of arsenic for the treatment of psoriasis. It is very doubtful whether the drug is of any value in this disease, because psoriasis is a chronic, incurable condition, and whatever benefit may be obtained from the use of Fowler's solution can be of only a temporary nature. Consequently, it should not be used as a routine treatment in this disease. It is not uncommon for keratoses which result from the ingestion of arsenic to appear several years after the use of the drug has been discontinued. This is quite characteristic of the condition.

The treatment of these keratoses is unsatisfactory. They do not respond to the administration of sodium thiosulphate which has been used so extensively in recent years in the treatment of dermatitis resulting from the organic arsenicals. If any of the lesions become larger, thickened, fissured, or ulcerated, they should be removed surgically or destroyed by electrodesiccation. The patient should not be frightened unduly about the possibility of malignant degeneration of these benign lesions, but he should be informed of the common signs suggestive of early malignant degeneration. If the patient is cognizant of these signs, he need not be alarmed. A malignancy which develops in an arsenical keratosis is usually of a low grade, and if removed early, good prognosis is offered.

The subject of drug eruption is one of tremendous scope. Much could be written on any phase of the subject and many questions concerning the nature and mechanism of the production of drug eruptions,

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as well as the reason for individual susceptibility to particular drugs, are still unsolved. The purpose of such a brief discussion as this is the desire to emphasize the importance of keeping in mind the possibility of drugs as etiologic factors in many dermatological cases.

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## CHOLECYSTOGRAPHY

E. N. COLLINS, M.D.

In the last decade, it has been found that cholecystography is the most important single objective aid in the diagnosis of dysfunction or disease of the gallbladder, yet neither the evaluation nor the technique of this procedure has become standardized. Early in the development of this test, Nichols, after a consideration of certain fundamental principles, adopted a procedure which has stood the test of time, i. e., the oral method of administration of the dye combined with roentgen examination of the entire gastro-intestinal tract, which often is preceded by an examination of the urinary tract. These same procedures are used today—10 years later—and in the patients who have had operations at the Cleveland Clinic during the past five years, this procedure has proved accurate, whether in a positive or negative way, in 95 per cent of the cases. The purpose of this brief discussion is to present the features of this examination, which in our experience have been of the greatest value.

There have been countless discussions relative to the merits of the intravenous versus the oral method of administration of the dye, and now that the oral method has been adopted generally, the current discussions center on the merits of the single versus the double or fractional dose method of administration.

Formerly, importance was attached to the time required for the gallbladder to fill and empty after administration of the dye. Now, Stewart and Illick<sup>1</sup> report that their best visualization of the gallbladder is on the film made 40 hours after fractional administration of the dye is started. Most observers take films after the fat meal only for the purpose of disclosing gall stones or small tumors which might be obscured in the completely distended gallbladder. We have followed the latter procedure at various times but have failed to find evidence of any abnormality which was not disclosed when the gallbladder was completely distended or on the 24-hour film following examination of the stomach after the barium meal (combined method). We have found that either the gallbladder fails to empty completely or there is sufficient reabsorption of the dye by the time this 24-hour film is made to exclude any abnormality which might otherwise be missed. The choice of method depends somewhat on the time available for the examination, and our aim is to make the examinations which will be of the greatest practical benefit to the patient per unit of available time. Of course, if several days spent in doing a cholecystographic examination alone proves to be a superior method with practical significance, present methods will be altered accordingly.



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A diagnosis of biliary disease can be made by cholecystographic examination alone, irrespective of the patient's symptoms, when it reveals the presence of gall stones, calcific deposits in the wall of the gallbladder, opaque bile in the gallbladder which is due to the presence of calcium carbonate<sup>2</sup> or of papillomas or other tumor<sup>3,4,5</sup> in the gallbladder. But, unless there is a history of definite biliary colic, care should be used in ascribing this evidence as the cause of the patient's presenting symptoms unless a complete examination has excluded abnormality in adjacent organs.

In the absence of unquestioned biliary colic, the expression "typical biliary symptoms" needs close analysis. It often refers to vague indigestion or distress in the epigastrium or in the right upper abdominal quadrant which is associated with belching and bloating and which comes on soon after eating. Although these symptoms are found in patients who have biliary disease, including those who also have biliary colic, the same symptoms may be produced by abnormalities in adjacent organs. In our experience, the most frequent cause for these indefinite symptoms is a *functional* disturbance in the colon, particularly in patients who have had constipation or diarrhea, or one alternating with the other for a long time, and in whom catharsis or irritating enemas may be the etiologic factor. When a complete examination excludes the possibility of organic disease, and this frequently includes examination of the stool and proctoscopic examinations, we ascribe the condition to "irritable colon," a term originated by the late B. W. Sippy. Our experience coincides with that of Palmer<sup>6</sup> who believes that this so-called "gallbladder dyspepsia" is in reality independent of the gallbladder, and that it is not unlike the dyspepsia which occurs in patients who are not afflicted with cholecystic or other forms of organic disease.

It is generally agreed that biliary disease is the most common *organic* cause of chronic gastro-intestinal symptoms in a middle-aged person. Routine autopsies both here and abroad <sup>7,8,9</sup> show that more than half of the adults past 30 years of age had abnormal gallbladders and that approximately one-fifth had gall stones. However, the relatively low previous clinical evidence of biliary disease in the latter group makes one question the advisability of prescribing surgery on cholecystographic evidence alone. Emphasis should be placed on the fact that operations on the biliary tract are now seldom advised unless there is positive clinical as well as cholecystographic evidence. Nichols<sup>10</sup> has emphasized repeatedly the fact that since the sympathetic nervous system, through the superior and inferior mesenteric ganglia, receives fibers not only from the gallbladder, but also from the stomach, duodenum, right kidney, ureter, and colon, pain or distress in the

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right upper abdominal quadrant may be due to abnormalities in any one or several organs.

In the absence of a history of unquestioned biliary colic, the possibility that organic causes for the patient's symptoms may originate in the urinary tract should have more general recognition. Urinary calculi as a cause of gastro-intestinal symptoms, particularly nausea and vomiting as well as pain, is well known. Patients have been operated upon for appendicitis or even intestinal obstruction when the trouble was in the urinary tract. Normal findings in examinations of the urine do not exclude abnormalities in the urinary tract. In our cases of hypernephroma, the incidence of hematuria has not been greater than 50 per cent. Thirty-four per cent of our patients with hydronephrosis have had previous abdominal operations without relief from symptoms. Although hydronephrosis due to aberrant blood vessels apparently is a rare condition, it may simulate biliary disease, and almost invariably normal urinary findings are revealed at examination. In 19 per cent of a series of cases of kidney tumor, there was no history which was indicative of disease of the urinary tract. With the above facts in mind, the basis for our view that the diagnosis of disease of the gastro-intestinal tract is largely a matter of exclusion, is obvious.

Unless the cholecystographic examination gives definite evidence of biliary disease, as mentioned above, how may the findings of this examination alone be evaluated? A normally functioning gallbladder may be pathologic even though stones are not present. Kirklin<sup>11,12</sup> has found this to be true in from 10 to 12 per cent of the patients who have had operations. It would seem logical to believe that the routine use of the double-dose or fractional method of administering the dye would increase this error, while the use of the smallest possible adequate dose should decrease this error. We should not forget that pathologic gallbladders which are filled with gall stones, commonly function normally with cholecystographic dye. Hence, cholecystographic evidence of a normally functioning gallbladder does not exclude the possibility of a pathologic gallbladder. On the other hand, we believe that in the presence of a normally functioning gallbladder in which there is no evidence of calculi, convincing clinical evidence is required before surgical interference is warranted.

When the cholecystogram results in non-visualization of the gallbladder without evidence of opaque calculi, the diagnosis of biliary disease is not warranted unless there is a suggestive history and all other possible causes for the symptoms have been excluded by a complete examination. It is true that this finding often indicates a non-functioning gallbladder which contains non-opaque (cholesterin type) stones, in which the cystic duct is blocked. But the possibility of other causes of

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non-visualization must receive due consideration, such as diseases of the liver or diseases in adjacent organs which may cause a reflex disturbance in the dye-concentrating ability of the gallbladder at least at the time the examination is made. The presence of hepatitis or other causes for diminished liver function is an obvious reason for non-visualization of the gallbladder by cholecystogram. Patients who have not had a roentgen examination of the stomach but who had "suggestive symptoms" plus non-visualization of the gallbladder by cholecystogram, have been found at operation to have a penetrating ulcer on the posterior wall of the duodenum. In our experience, the presence of an early non-obstructing carcinoma of the stomach often causes non-visualization of the gallbladder by cholecystogram, even though operation reveals no evidence of metastasis in the liver. We have had patients in whom the only disorder to which we could attribute non-visualization of the gallbladder was a functional disturbance of the colon which was mentioned above. When the latter condition was improved by the use of a bland, low-residue diet, general hygienic measures, such as rest, adequate sleep and exercise, and restoration of normal bowel function, a subsequent examination revealed normal cholecystographic findings. Hence, cholecystographic evidence of a normally functioning gallbladder does not exclude a pathologic gallbladder, nor does non-visualization always indicate a pathologic gallbladder. At the same time, when the cholecystograms reveal definite impairment of function of the gallbladder, the absence of symptoms does not preclude the existence of biliary disease, for the clinician realizes that "silent gall stones" are not mythical, and that often they are disclosed only by cholecystography.<sup>13</sup>

We believe the only solution of these many and often perplexing questions is the proper evaluation of the history of the patient's symptoms, plus a complete roentgen examination of all organs which may cause these symptoms. If the pain or distress is in the right upper abdominal quadrant but if it is not "typical" for biliary disease, we believe an investigation of the urinary tract should be the first special examination, before barium is administered, regardless of normal urinary findings. A stereo-roentgenographic study of the urinary tract is made, and from the roentgen standpoint, intravenous urograms or a retrograde pyelogram may be necessary for exclusion of disease in the urinary tract.

After the urinary tract is excluded as a cause for the patient's symptoms, roentgen examinations of the gallbladder, stomach, small intestine, and colon are made. Plain stereo-roentgenograms of the gallbladder always are made before the dye is administered. The single dose, oral method is used as a routine procedure, but in those patients

in whom the gallbladder is not visualized, a second dose is given the following evening even though the stomach and small intestine have been examined in the meantime. In those patients to whom dye is administered a second time, the barium enema is delayed the following morning until sufficient time for visualization of the gallbladder has elapsed. On a rare occasion, where the findings are still questionable, we advise a re-check cholecystogram after medical treatment has been administered for one month or longer.

The patient takes the dye immediately after a full-sized evening meal, from which only butter, cream, and other fats are omitted. Various forms and amounts of the dye, and various medications have been used with the dye, but in our hands, the plain dye taken in grape juice or other fruit juices has caused the patient the least discomfort and has given the most satisfactory results from the standpoint of absorption of the dye. The druggist places 5 grams of sodium tetraiodophenolphthalein in a colored bottle which holds one ounce, adds  $1\frac{1}{2}$  drachms of paregoric, fills the bottle with distilled water and shakes it just before handing to patient (the dye must be freshly prepared when given in this way). The patient empties the contents of the bottle into a glass containing 4 ounces of grape juice or other fruit juice, stirs thoroughly, and drinks it all quickly.

The following morning only black coffee or clear tea is permitted, and the first cholecystograms are taken at 9 o'clock. If the cholecystograms show normal visualization of the gallbladder, we routinely proceed at once to the roentgen examination of the stomach. If not, we take further cholecystograms at 11 o'clock and then start the stomach examination, regardless of the cholecystographic findings. The simultaneous visualization, both fluoroscopically and on films of the position and mobility of the gallbladder as related to the stomach and duodenum, has proved a valuable procedure of itself. When the cholecystograms as well as the stomach films are interpreted in conjunction with the fluoroscopic findings, if the evidence is not conclusive, further films are taken at 3 p. m. at the time of the retention studies. Using this method, this 21-hour film often shows our best visualization of the gallbladder. If it is thought advisable, a fat meal then is given and the patient is asked to return for further cholecystograms, but this is not done as a routine procedure. Usually after the retention studies, the patient is advised to eat as usual and to return the next morning for the 24-hour study (subsequent to the barium meal administration) and barium enema examination. As already mentioned, the 24-hour film or the film taken after the expulsion of the enema often shows sufficient dye in the gallbladder to reveal a gall stone or tumor which might have been obscured in the completely distended gallbladder.

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Other attempts at the study of the partially emptied gallbladder without taking a separate day for cholecystography alone, have been made by giving cream with the barium meal used in the stomach examination. This results in visualization of a contracted gallbladder on the retention film, but, as mentioned above, the best visualization of the fully distended gallbladder at retention time when the cream is not used is sacrificed. For a time, we used 15 to 30 cc. of a mixture of egg yolk, lecithin, glycerine and alcohol, as recommended by Levyn<sup>14</sup> immediately after the gallbladder was visualized, which was followed by additional cholecystograms before examination of the stomach was begun. This procedure did not interfere with the efficiency of the latter examination, but the delay in the starting time occasionally resulted in interference with desirable retention studies of the stomach. We do not believe the use of these procedures increased the accuracy of the cholecystographic examination.

It is agreed by all that attention to details of technique is essential, and this has been emphasized repeatedly by Kirklin.<sup>11</sup> We have not required patients to take enemas routinely on the morning of the examination because the results were disappointing. When black coffee is taken in the morning, it seems to reduce the incidence of intestinal gas in the right upper quadrant, but if this still remains a troublesome feature, films are taken in different respiratory phases at later intervals, or a small anterior-posterior kidney film is taken. This changes the position of the gallbladder upward and outward and has been used by Nichols for years, particularly in the differentiation of gall stones from kidney stones when the appearance or location of the calcification is questionable. From a consideration of x-ray physics, it is realized that if the calcification is in or near the gallbladder it will be smaller and more distinct on the posterior-anterior gallbladder film, whereas if it is in or near the kidney it will be smaller and more distinct on the anterior-posterior kidney film.

## CONCLUSIONS

1. In making a diagnosis of biliary disease, unless a patient gives a history of unquestionable biliary colic, the exclusion of abnormality in adjacent organs is equal to if not of more importance than the cholecystographic examination alone.
2. Although a diagnosis of biliary disease can be made from the cholecystographic data alone, regardless of the symptoms, care should be used in ascribing this evidence as the cause of the patient's presenting symptoms.
3. Non-visualization of the gallbladder by cholecystogram does not warrant the diagnosis of biliary disease unless the symptoms are

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suggestive, and unless all other possible causes for the symptoms have been excluded by a complete examination.

4. A method of examination which has proved satisfactory during the past 10 years is described.

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## INDIVIDUALIZATION OF THE PATIENT IN THE TREATMENT OF HYPERTHYROIDISM

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### I. INTRODUCTION

The association of hyperthyroidism with old age, extreme youth, heart disease, substernal goiter, or a poor preoperative response of the pulse curve, and with certain complicating diseases, presents a different problem in each instance from the standpoint of surgical treatment. Since it is not possible to set up a routine which is applicable to the management of every case of hyperthyroidism, patients in each of the groups mentioned should be given individual consideration. In short, the problem of the relative prognostic significance of the various factors which constitute warnings in patients with hyperthyroidism will be studied in regard to the specific complications which must be guarded against in each group of patients.

### II. TREATMENT OF THYROID CRISIS

It is extremely significant that in the past 10 years, exactly one-half as many patients have died from hyperthyroidism in the Cleveland Clinic Hospital before any operative procedure had been undertaken as have died following operation for hyperthyroidism. This means that the hyperthyroidism which we see has advanced in many instances beyond the stage of curability.

Fifty-eight per cent of these patients who died in the hospital without operation died as a result of thyroid crisis, and ninety-four per cent of the patients who died from thyroid crisis without operation were delirious when they were admitted and died within five days of the time of entry. These figures indicate that if a patient in crisis survives the reaction incident to transportation to the hospital, there is a 94 per cent chance for her recovery. It can be assumed, therefore, that transportation aggravates a thyroid crisis and that a patient already in thyroid crisis should not be transported until the hyperthyroidism is controlled.

In the majority of the cases of fatal preoperative thyroid crisis, long-standing medical treatment had been attempted and often, x-ray or radium treatment had been tried unsuccessfully in the hope that an operation might be avoided. Often an acute infection of the upper respiratory tract or radiation therapy was the precipitating cause of the crisis. These facts emphasize the importance of prompt operation after a definite diagnosis of hyperthyroidism has been made.

Patients who are admitted in thyroid crisis should be given iodine by mouth, or, if the patient is vomiting, iodine should be given by

rectum in doses as great as 30 cc. of Lugol's solution a day. A 10 per cent solution of glucose to which iodine may be added is of great value in combating the tendency to dehydration and acidosis which often is present in patients in thyroid crises.

In a thyroid crisis, a vicious circle of excess metabolism and increase of temperature is present. The elevation of temperature increases the metabolism 7.2 per cent for every degree of temperature centigrade, and the increased metabolism results in greater heat production, and hence in a further elevation of the temperature. By refrigeration, this cycle can often be overcome and the temperature reduced to normal. For this reason, the oxygen tent is a valuable therapeutic agent in the treatment of thyroid crisis. Frequently, the temperature drops several degrees within a few hours of the time of its introduction. It is difficult to say whether this is the direct result of the oxygen or of the refrigeration from the cooled air, but the prompt benefit which the patient appears to experience suggests that the oxygen itself plays a significant rôle in combating anoxemia secondary to excessive metabolism and a failing myocardium. Refrigeration in the form of ice packs should be applied when the temperature is above 102° F. by mouth.

Complete digitalization should, of course, be carried out at once when auricular fibrillation or cardiac decompensation is present. It is extremely important for the patient to obtain rest from the wild and exhausting delirium which often is present. To accomplish this, bromides and morphine are of much more value as sedatives than the barbiturates, and this is true particularly in the older patients who not infrequently become maniacal following the administration of amytal, phenobarbital, etc.

Blood transfusion should be prescribed with caution when the temperature is at its peak. A transfusion reaction may occur as a result of the increased susceptibility of patients with high temperatures to such reactions. However, transfusion is of great value, particularly in elderly patients when the temperature is not too high and when longstanding hyperthyroidism, as is so often the case, has resulted in a lowering of the serum proteins and the production of edema.

### III. ROUTINE PREOPERATIVE TREATMENT OF HYPERTHYROIDISM

The routine preoperative management of the patient with hyperthyroidism consists in absolute bed rest, quiet surroundings with limitation of visitors, 30 grains of sodium bromide once or twice daily, mild hypnotics at night, and iodine in the form of 1 cc. of Lugol's solution three times daily. The patient should not be told the date of operation because almost invariably if this is done, it will be found that a night of worry will follow and the pulse rate will be elevated above its usual

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level on the morning of the operation. One of us, in the earlier days of thyroid surgery, has seen a fatal thyroid crisis precipitated by informing a patient with severe hyperthyroidism of the date of operation, taking her to the operating room fully conscious, and then returning her to the ward without having administered any anesthetic or performed any operation. Therefore, operation is performed in the patient's room without any warning or preliminary psychic disturbance.

### IV. CHOICE OF TIME OF OPERATION, TYPE OF OPERATION, AND ANESTHETIC

#### *a. Indications of Unfavorable Prognosis*

No standard time of operation, no standard type of operation, and no standard anesthetic should be employed in the operative treatment of patients with hyperthyroidism. Each case should be individualized on its own merits, and the time and the type of operation and the anesthetic should be planned according to the prognosis of the case. In this way only can the maximum safety be assured to the bad risk case, and the minimum hospitalization and discomfort guaranteed to the patient for whom thyroidectomy should present no especial hazard.

The only two absolute contraindications for the surgical treatment of hyperthyroidism are persistent delirium or persistent vomiting. There are, however, certain factors whose presence, although they do not contraindicate surgery, constitutes a warning of an unfavorable prognosis.

In order to determine the relative prognostic significance of the various factors which generally are considered to constitute warnings, an analysis of the fatalities which followed operations for hyperthyroidism in the years from 1924 through 1934 has been made. If these warnings are classified according to the ratio of their occurrence in the group of patients who died following operation as compared to an equal number of patients in each year who were picked at random from those who survived operation, it is found that cardiac complications stand first in importance, and that auricular fibrillation, cardiac decompensation, myocarditis or valvular heart disease occurred seven times as frequently in the patients who died as in those who survived operation. Substernal goiter was present in a ratio of 6:1, a flat pulse curve in a ratio of slightly over 5:1, and age over 60 was present in a ratio of 5:1. The ratio of the presence of severe hyperthyroidism (Grades III and IV) was 3:1. Pulse over 100 at the time of operation was 2.5:1; the presence of complicating diseases, tuberculosis, diabetes, etc., but not including cardiac disorders was in a ratio of 2.5:1; pulse over 120 at entry was 2:1; weight loss of over one-fifth the body weight was 2:1. An analysis of all other factors, such as the presence of

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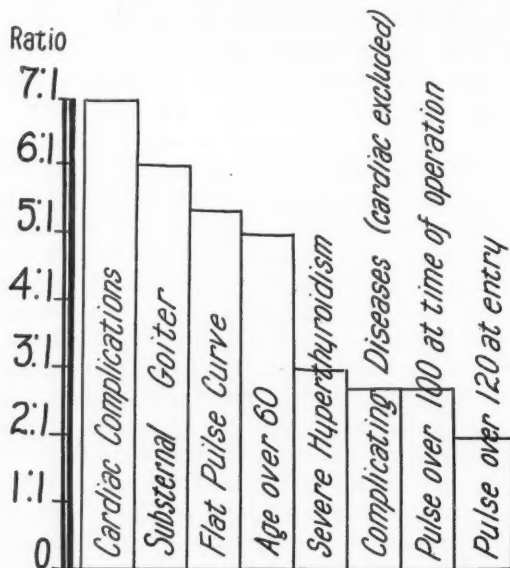
nodular goiter, of a hyperplastic goiter, of preoperative irradiation, of duration of the disease for more than two years, of a history of iodine medication before entry, of a basal metabolic rate above plus 50 per cent, and of sex showed that each occurred as frequently in the patients who survived operation as in those who died following operation (Chart 1).

In the order of frequency with which these warnings of the fatal outcome occurred, we find that age over 50 stands first, severe (Grades

Chart 1

Relative Importance  
of Various Warnings

(Figures based on ratio of incidence of special warnings in patients who died following operation, to their incidence in patients who survived operation)

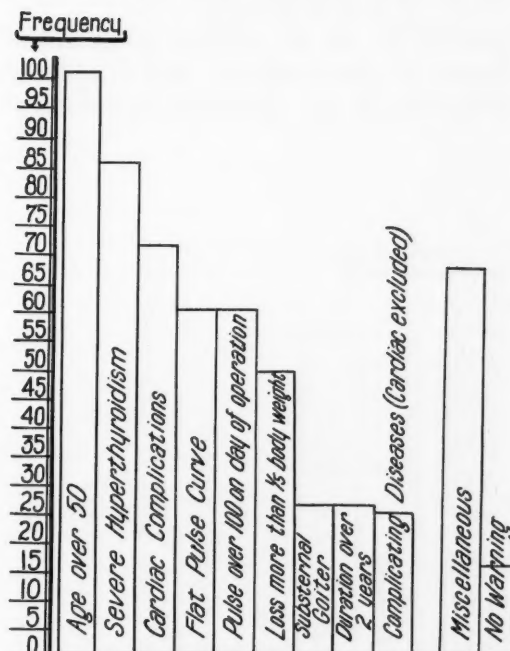


## INDIVIDUALIZATION IN TREATMENT OF HYPERTHYROIDISM

III and IV) hyperthyroidism second, cardiac complications third, the presence of a flat pulse curve (in effect a pulse curve which does not fall as rapidly as expected under the preoperative treatment) fourth, pulse over 100 on the day of operation fifth, loss of over one-fifth of the body weight sixth, the presence of a substernal goiter seventh, duration of the disease for more than two years eighth, and the presence of complicating diseases (exclusive of cardiac disorders) ninth (Chart 2).

Chart 2

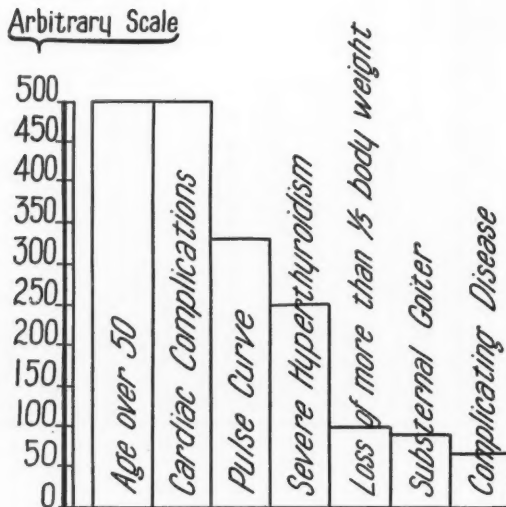
### Frequency of Occurrence of Special Warnings



From these figures which represent (1) the frequency of the occurrence of each warning and (2) the ratio of incidence of each warning in patients who died after operation to its incidence in those who survived operation, we can build an arbitrary scale which indicates the probable importance of these various warnings in operative prognosis (Chart 3). It is our belief, however, that in spite of these figures which place age on a par with cardiac disease, age should stand first, because in the majority of instances, a cardiac disorder is the direct result of the arteriosclerotic processes that come with advancing years. Although the presence of a substernal goiter appears to be of little significance on the arbitrary scale, we believe that when this complication is present, it is of definite prognostic importance because it occurred six times more frequently in patients who died following operation than in those who survived operation.

Chart 3

Relative Importance of Various Warnings on an Arbitrary Scale Based on the Incidence and Prognostic Importance of Specific Warnings





## INDIVIDUALIZATION IN TREATMENT OF HYPERTHYROIDISM

Our final evaluation of these prognostic factors in the order of their importance is therefore (1) age, (2) cardiac condition, (3) pulse curve, (4) severity of hyperthyroidism, (5) substernal goiter, (6) loss of weight, and (7) complicating diseases (Chart 4). The final criterion on which we base the contention that age is the most significant prognostic factor is the fact that we have been able to perform as many as 1758 consecutive operations on patients under 45 years of age without a single fatality.

Despite the general conception that a history of long duration of the disease, a history of iodine therapy, or a high basal metabolic rate constitute danger signs, we have not, in this analysis, been able to find supportive evidence for such opinions. The average basal metabolic rate of the patients who survived operation was only 3.4 per cent higher than that of those who died after operation; moreover, the incidence of the basal metabolic rates above plus 50 per cent was nearly twice as great in the survivors as in the dead.

### *b. Determination of the Time of Operation*

The time of operation is determined by the evaluation of the risk of the patient as judged by the presence or absence of the above warnings. The exact date is never set until the night before the operation, and should the patient's pulse rate on the morning of operation be elevated above its usual level, the operation is postponed. Under these conditions, the preoperative routine should be continued until the pulse curve has responded satisfactorily. In cases in which this curve is flat and does not come down in response to the preoperative routine, the minimum operation should be performed, and this should be performed only after prolonged observation of even three or four weeks has shown that the pulse rate will not fall below 100 in spite of adequate treatment. In this type of case, although the pulse may be only 100, the prognosis unquestionably is less favorable than in cases in which the pulse rate is higher but the drop in the pulse curve has been abrupt.

### *c. Choice of Operation*

The minimum operation which is reserved for those patients who are judged to be the worst risks, is a single "trial ligation" of the superior thyroid artery under local anesthesia. If the reaction from this ligation is minimal, it is a good indication that the patient will be able to withstand a more extensive procedure, and that in a few days, a lobectomy can be performed with safety. If, however, the patient has a marked reaction following the ligation, it is best to wait until this reaction has subsided and then ligate the artery on the other side. The patient then is sent home to rest for three months, at the end of which period she returns for the completion of the operation.

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If a lobectomy is performed, the wound is packed open with acroflavin gauze until the next morning. At this time, if the patient's condition is satisfactory, the second lobe is removed, thus completing the operation at one hospitalization. If, however, the reaction has been severe, the incision is closed, and the patient is sent home for three months before the other lobe is removed. It is interesting to note that we never have lost a patient following the second lobectomy when the patient has been sent home between the stages of the operation. Thus, when lobectomies are performed three months apart, even though it may seem inconvenient to the patient, it constitutes the safest method of thyroidectomy. One stage thyroidectomy, of course, is performed in the great majority of cases (85.7 per cent) and the above procedures are reserved only for those cases which present especial operative hazards.

### *d. Choice of Anesthetic*

The choice of the anesthetic necessitates careful study, not only of the objective findings in the case, but also of the patient's personality, mentality, and emotional control. There can be no question but that when a local anesthetic is administered to an extremely nervous and emotionally uncontrolled patient, a psychic reaction occurs which may be more alarming than the depression which follows some types of general anesthesia. However, in the majority of cases, adequate and skillful infiltration of the local anesthetic supplemented by gas oxygen analgesia can make the operation so completely devoid of sensation that thyroidectomy can be performed without "psychic trauma." A basal anesthesia of 60 milligrams of avertin per kilogram of body weight has been used in selected cases since 1932 with good results.

A wide block with local anesthetic (three-fourths of one per cent novocain) supplemented with gas oxygen analgesia results in the ideal anesthesia for those patients who are cooperative and have good emotional control. These patients are carried in a stage of pleasant unconcern in which they are led by the anesthetist to discuss any subject that will divert their attention from the operation. This, of course, can be accomplished without depression of respiration and intracellular metabolism, and hence without the increased operative risk that necessarily accompanies a general anesthesia.

### *e. Management of the Patient between Stages of a Divided Operation*

In the management of patients who are sent home between stages of a divided operation, either following ligations or between lobectomies, it is important to bear in mind the possibility that if iodine medication has been administered for a long time before the patient

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entered the hospital, the disease may be partially under control and may actually be more severe than is apparent clinically. Therefore, if the patient is sent home following, for example, a ligation, and iodine is withdrawn, it is possible that an exacerbation of the hyperthyroidism may occur incident to the withdrawal of iodine, and that this exacerbation may be more severe than the remission induced by the ligations. If this is the case, a thyroid crisis may ensue at home, or the patient may go on to cardiac decompensation. We believe, therefore, that following the first stage of a divided operation, iodine should be administered until the remission induced by the operation is well established, and that it should then be withdrawn so that for the final six weeks before re-admission, the patient will have had no iodine and hence will be susceptible to iodine control. We believe that iodine loses its maximum effectiveness after protracted use, and although iodine undoubtedly does exert a slight effect in the control of hyperthyroidism for an indefinite period of time, the maximum benefit occurs in from two to four weeks. After this period, the continued use of iodine may be followed by the phenomenon of "iodine escape" and an exacerbation of the hyperthyroidism. For this reason the use of iodine is discontinued six weeks before the patient returns for the completion of the operation so that the maximum preoperative response to iodine may be attained.

### V. DISCUSSION OF EFFICACY OF SPECIFIC AGENTS IN THE PROPHYLAXIS AND TREATMENT OF COMPLICATIONS

Iodine, refrigeration, intravenous glucose, and blood transfusions are all indicated in the management of a postoperative thyroid reaction in exactly the same way as they are in the management of a thyroid crisis.

Preoperative digitalization is reserved for those patients who show evidences of myocardial failure or who have auricular fibrillation. We believe that it is not necessary to administer digitalis routinely to every patient before operation.

Since 1930, bad-risk patients have been placed in an oxygen tent immediately following operation and kept there until the reaction has begun to subside. We believe that this procedure has resulted in a definite reduction in the incidence of thyroid crisis. As mentioned before, it is difficult to state definitely whether or not much of this effect is not the result of refrigeration. During the past 10 years, there have been, on the average, twice as many deaths from thyroid crisis during the hot months of the year—June, July, and August—as in the colder period of the year. This in itself shows the necessity for refrigeration. But the oxygen tent appears, as above stated, to have a more specific effect on the thyroid reaction. The incidence of pneumonia

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has not diminished as a result of the prophylactic use of the oxygen tent, but the relative incidence of mortality from pneumonia has diminished 50 per cent since its use was adopted in 1930.

VI. APPLICATION OF SPECIFIC THERAPEUTIC MEASURES  
TO SPECIAL GROUPS

We have mentioned the various factors which constitute warnings in regard to operative risk and have discussed the therapeutic measures by which these risks can be minimized. The question next arises as to how we can apply these therapeutic measures to specific groups of patients so that the individual patient will have the maximum safeguard against the complications which occur most commonly in her specific group.

Further analysis of the cases which have terminated fatally following thyroidectomy shows that the presence of a flat pulse curve, of a basal metabolic rate of over plus 50 per cent, of a psychosis, or of severe hyperthyroidism, especially in young patients, constitutes a special warning against the development of the postoperative thyroid crisis which is the commonest cause of death in patients in these groups. In substernal goiter and in old age, the greatest risk is pneumonia. Myocardial failure is the most frequent cause of death in patients with auricular fibrillation, cardiac decompensation or evidences of chronic myocardial damage and also in those patients in whom the disease has been present for more than two years, and in those with low grade hyperthyroidism (Chart 4).

*a. Severe Hyperthyroidism*

In the first group—those patients who have an excessively high basal metabolic rate, a flat pulse curve, or in those who have a psychosis—all our therapeutic measures against thyroid crisis including blood transfusion, parenteral fluids, the oxygen tent, and morphine in doses sufficient to insure comfort and rest, should be used immediately following the operation.

While we believe that small amounts of iodine should always be continued after operation, we never have felt that the postoperative use of large doses of iodine exerted any striking effect on the thyroid reaction of a patient who had received the maximum amount of iodine. One of us has shown in the experimental laboratory that the administration of iodine exerts no effect on the elevated metabolism of completely thyroidectomized dogs fed on large quantities of desiccated thyroid. The effect of iodine is, therefore, not on the tissues of the body in general or on the thyroid hormone circulating in the blood, but its action is rather directly on the secretory activity of the thyroid gland. For this reason, large doses of iodine cannot be expected to cause any effect on

# INDIVIDUALIZATION IN TREATMENT OF HYPERTHYROIDISM

Chart 4  
Causes of Death in Patients with Specific Warnings

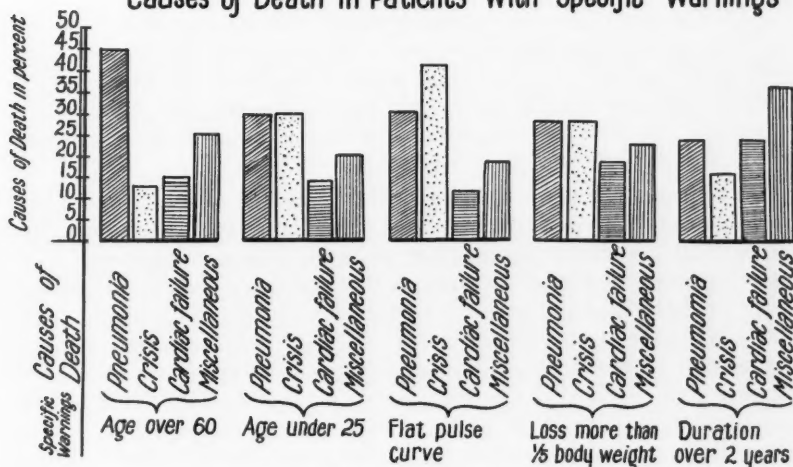
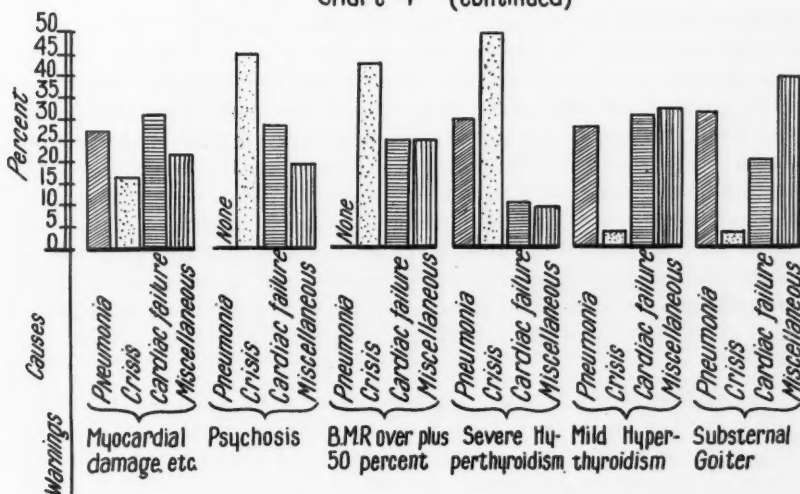


Chart 4 (continued)



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the postoperative reaction of a fully iodized patient. The best we can do is to carry on with the routine small dose of iodine so that at least there will be no exacerbation of symptoms incident to the withdrawal of iodine.

If the surgeon believes that the patient's greatest hazard is from the severity of the hyperthyroidism and if the patient is relatively young and otherwise in good condition, a basal anesthesia of avertin is of definite value in calming the patient and minimizing the postoperative reaction. If, however, the patient is old or debilitated, the use of this drug is contraindicated as will be explained later.

In all cases, the temperature should be watched carefully and taken at least every two hours during the first two days after operation. This is particularly true in hot weather when the rise of the patient's temperature may be almost as rapid as that following a chill. If 12 ice caps are placed on the patient's extremities and about the sides of the body when the temperature reaches 102° F., its further elevation can usually be controlled. Additional ice caps are added and an alcohol sponge bath is given if the temperature reaches 103° F. If it should continue to rise to 104° F. or above despite these measures, the patient literally is packed in cracked ice so that more heat is abstracted than can be created. In this way only can the patient be saved from "burning herself up" in a crisis of chemical hypermetabolism.

*b. Hyperthyroidism in Old Age*

The management of the aged patient, in whom pneumonia is the greatest hazard, is quite different. We have seen that sedation and avoidance of psychic disturbances are fundamental principles in the management of severe hyperthyroidism in the young adult. But in the aged, we must not depress the respiration or the internal metabolism of the body because of the danger of inducing a terminal pneumonia. Depressant drugs are tolerated well in the young but easily force the aged below the critical threshold at which resistance cannot overcome the ever-present tendency to pneumonia. Every resource at our disposal must be utilized to build up the resistance of the aged patient and stimulate the vital functions. Preoperative and postoperative blood transfusions are of especial value in the aged, and there can be no question as to their value in increasing the resistance and strength of the patient.

As we have shown already, the chief hazard in the aged is pneumonia, while death from thyroid crisis is relatively rare. Hence, in the aged, it is better to perform the operation under local anesthesia with a minimum of gas oxygen analgesia. Avertin or any general anesthesia with its secondary depression of respiration, the cough reflex, and of the internal metabolism should be avoided even at the expense of an occa-



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sional mild psychic reaction. Similarly, the postoperative use of morphine should be limited to the minimum requirements.

In old age, the principle of the multiple stage operation should be followed, and a trial ligation should be performed if there is any question in the mind of the surgeon in regard to the ability of the patient to withstand a more radical procedure. Pneumonia may follow even a relatively mild thyroid reaction, and the general condition of the patient as well as her status in regard to hyperthyroidism, should be given prime consideration in the choice of both the time and type of operation.

As has been shown before, the use of the oxygen tent has lessened the mortality rate from pneumonia. The aged patient with hyperthyroidism therefore should have oxygen therapy at least as soon as any signs of pulmonary congestion occur. In addition, we believe that the severity of the thyroid reaction has been reduced by the use of the oxygen tent, and that bad-risk patients of all ages make better progress when oxygen therapy is started immediately after the operation.

In the aged, ice packs should be applied only when absolutely necessary so that chilling with its attendant liability to pulmonary complications may be avoided.

### *c. Hyperthyroidism with Cardiac Complications*

Preoperative digitalization, as we have mentioned above, should be reserved for those patients who show evidence of severe myocarditis, or who have auricular fibrillation or cardiac decompensation. As soon as either of the latter two complications are discovered, the patient should receive digitalis immediately. Oxygen therapy is of value in these cardiac complications as is morphine in doses adequate to insure rest. In this way, the failing myocardium is strengthened by the digitalis, the efficiency of the oxygen-distributing function of the heart is increased by the oxygen tent, and the metabolic demands of the organism as a whole are decreased by the morphine to the point that a balance between oxygen supply and demand is struck and cardiac compensation restored. Blood transfusion of course is contraindicated in the presence of acute cardiac decompensation.

### *d. Intrathoracic Goiter with Hyperthyroidism*

The presence of an intrathoracic goiter in a patient with hyperthyroidism demands special consideration. Pneumonia again is one of the greatest hazards and the same routine measures for its prevention should be applied as have been suggested for the prevention of pneumonia in the aged. The multiple stage operation, however, increases the technical difficulties in the removal of an intrathoracic goiter, and this type of operation is not performed except in cases in which it is felt that a one stage operation would involve an unjustifiable

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risk. The technical difficulties in the delivery of a substernal goiter may be increased enormously by adhesions and scar tissue secondary to the first stage of a divided operation.

*e. Hyperthyroidism Complicated by Chronic Nephritis*

In the presence of chronic nephritis, avertin should not be used. The patient should be treated before and after the operation with large quantities of a 10 per cent solution of glucose administered intravenously.

*f. Hyperthyroidism Complicated by Liver Damage*

When hyperthyroidism is complicated by liver damage, such as alcoholic cirrhosis, the chief cause of death is a peculiar type of toxemia which is characterized by stupor and alterations of the blood chemistry, which perhaps are incident to hepatic insufficiency. This complication is best averted by the pre- and postoperative administration of a high carbohydrate diet and large quantities of a 10 per cent glucose solution intravenously.

*g. Hyperthyroidism Complicated by Diabetes*

The postoperative management of the diabetic patient with hyperthyroidism may also be difficult and the attention of a competent specialist in diabetes is desirable. The most important principle involved is the constant maintenance of oxidation of relatively large quantities of glucose.

*h. Hyperthyroidism Complicated by Pulmonary Disease*

In the presence of chronic pulmonary disease, the incidence of postoperative pneumonia is high, and the same precautions which were recommended in the treatment of patients with substernal goiter with hyperthyroidism should be taken.

VII. CONCLUSIONS

1. The prophylaxis of postoperative complications in patients with hyperthyroidism is more important than treatment after such complications have developed.
2. An accurate knowledge of the postoperative complications to be expected in each type of case is essential if the proper prophylactic measures are to be taken before dangerous complications develop.
3. The recognition of the presence of certain warning factors is of value in prognosis and in the anticipation and prophylaxis of specific complications.
4. The surgical management of patients with hyperthyroidism should be based on an appreciation of the complications to be guarded against in each group of patients as well as a familiarity with the value of the specific forms of prophylaxis and therapy available for each group of patients.

## SPECIAL POINTS IN THE TECHNIQUE OF THYROID SURGERY

ROBERT S. DINSMORE, M.D.

A review of the literature on the technique of thyroid surgery brings one to the conclusion that many variations of technique exist and that all fulfill the requisites for the satisfactory removal of the thyroid gland. After all, a satisfactory technique is one which can be carried out within a reasonable length of time under some form of light anesthesia or analgesia augmented by local anesthesia; one in which the proper amount of the thyroid gland is removed without injury to the recurrent laryngeal nerves or to the parathyroid bodies; one in which

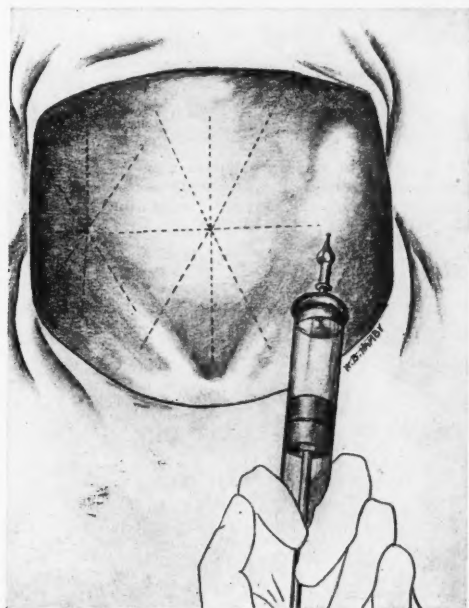


FIGURE 1.—Direction of infiltration with three-fourths per cent novocain. No attempt is made to inject beneath the fascia at the time.

satisfactory results are obtained from a cosmetic standpoint; and above all, one which brings about the cure of the patient.

The infiltration of novocain is carried out in three steps. The skin and subcutaneous tissue is first well blocked over a wide area. In this step, no attempt is made to infiltrate beneath the cervical fascia or in the preglandular muscles.

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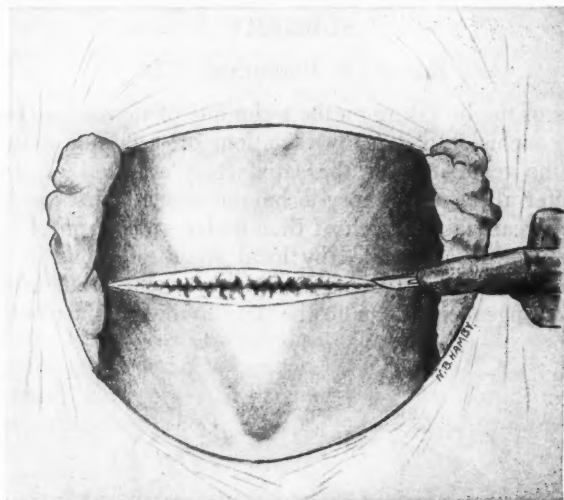


FIGURE 2.—Straight transverse incision across neck. The dissection is carried through the subcutaneous tissue and the platysma muscle down to the cervical fascia, thus making a full-thickness skin flap.

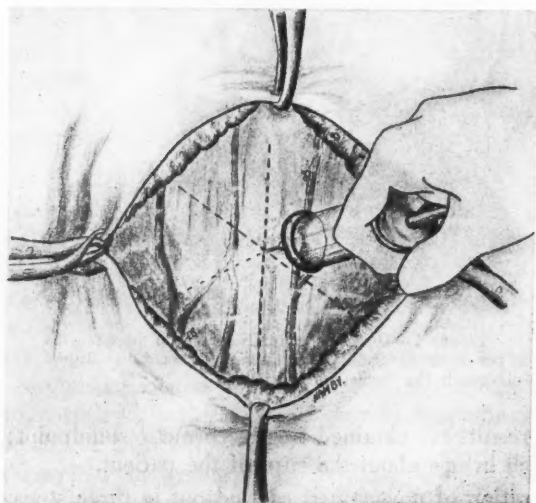


FIGURE 3.—After the dissection of the skin flaps, three-fourths per cent novocain is injected beneath the cervical fascia and into the preglandular muscles.

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For several years I have used a transverse incision, (Richter<sup>1</sup>) which is usually at a point about midway between the suprasternal notch and the cricoid cartilage. In my experience, this incision has produced the most satisfactory type of scar. Often, in making an elliptical inci-

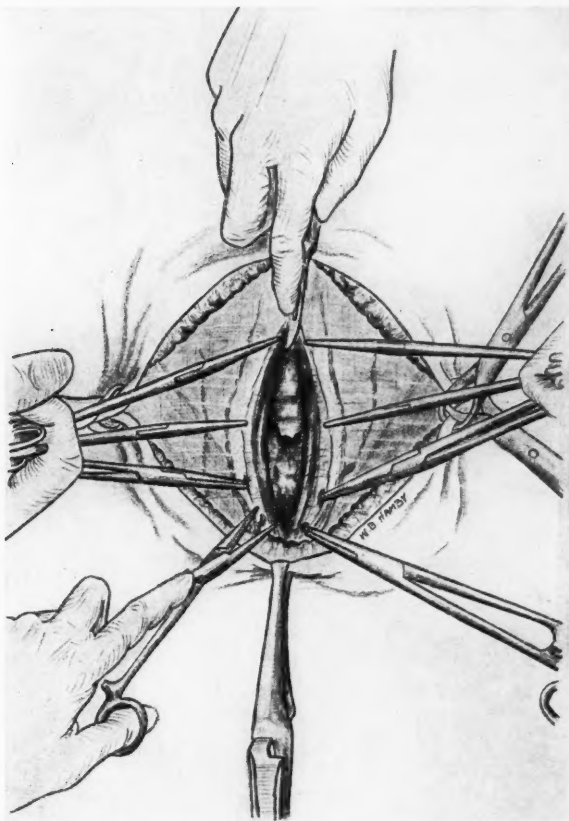


FIGURE 4.—Longitudinal incision through the fascia, pre-glandular muscles and capsule of the gland. This dissection is carried from the level of the cricoid cartilage well down into the suprasternal notch. With a long incision it is not necessary to divide the pre-glandular muscle transversely.

sion, one is surprised to find after the operation, that the ellipse is exaggerated because, at the time of operation the head was in extension and when the head drops down, the curve of the incision is increased. Also, in the elliptical incision, occasionally one is surprised to find that one end of the incision is slightly higher than the opposite one, while

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in the transverse incision, a slight ellipse is produced when the head drops down while this does not occur with the straight incision.

The incision is carried through the skin, the subcutaneous tissue, and the platysma muscle directly down to the cervical fascia. The upper

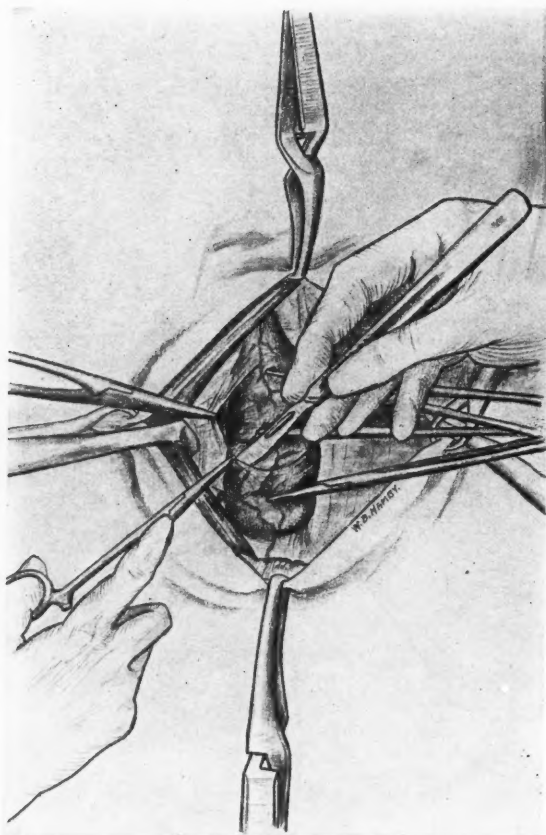


FIGURE 5.—The capsule of the gland is dissected cleanly from its surface laterally to the level at which the gland is to be divided. None of the capsule is removed.

skin flaps then are dissected up to the level of the cricoid cartilage, giving a thick skin flap. The dissection of the lower flap is carried well down to the suprasternal notch. These dissections must be carried a little farther than was the former practice, inasmuch as the pregladular muscles are not divided transversely and the linear incision in the



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midline through the fascia and preglandular muscles is carried from the cricoid to the suprasternal notch.

The cervical fascia and preglandular muscles are then infiltrated with novocain. The capsule of the thyroid is exposed and opened in the same line with the fascia and preglandular muscles. Care is taken that

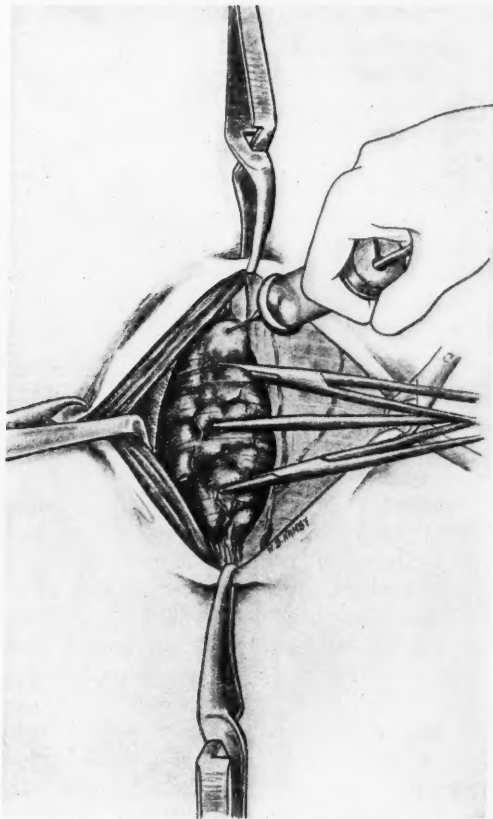


FIGURE 6.—After the gland has been exposed, the third infiltration is made and hemostat is applied for traction.

the capsule is dissected cleanly and that none of it is removed during the operation. I feel that this is extremely important in the prevention of parathyroid tetany, as I am certain that many parathyroid glands have been removed because the capsule was not dissected cleanly from the thyroid gland. After the gland is thus exposed, ordinary hemostats are used to elevate it. I have used various types of goiter clamps,

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all of which work very well in the adenomatous and colloid glands, but all of which also have a tendency to break through in the extremely friable and hyperplastic glands. These hemostats are inserted just within the true capsule of the gland.

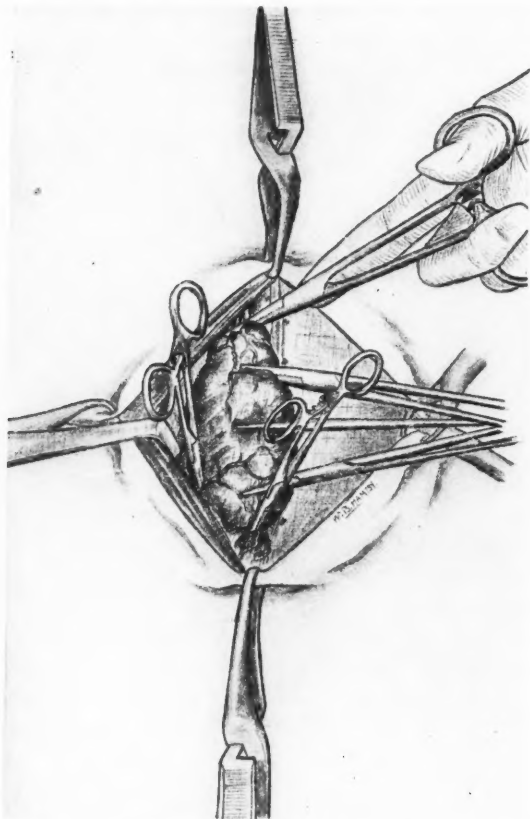


FIGURE 7.—Application of three pilot hemostats. The upper pole is dissected free and lifted up, the hemostat always being directed from within outward. The lateral vessels are caught with the second hemostat. The inferior pole then is caught, the clamp being applied so as to take up some thyroid tissue with it and to have the clamp standing erect.

After the gland has been exposed, the third step of the infiltration is carried out with 10 or 15 cc. of novocain which is injected into the gland itself. The major portion of this is injected at the upper pole, because most of the reflexes of pain apparently are transmitted through the upper pole and, therefore, this should be infiltrated carefully if the

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operation is performed under very light analgesia or local anesthesia. Retractors then are placed inside the cervical fascia and pregladular muscles, and the whole right lobe, if possible, is exposed. The ideal exposure is one in which you can see the superior thyroid vessels, the lateral thyroid vein, and the inferior thyroid vessels.

I have felt that it is quite important that three pilot hemostats be applied before any actual dissection is carried out. These should be applied accurately because many injuries to the recurrent laryngeal nerves can be avoided if care is used in this first step of the actual thyroidectomy. The upper pole of the thyroid ordinarily lies opposite the larynx, close to the point where the terminal branches of the recurrent laryngeal nerves enter the larynx. If the upper pole is separated carefully and the clamp applied from the inside out, these branches cannot be caught in the hemostat. On the other hand, if a clamp is placed from the outside without freeing the upper pole, it is very easy to injure one of the terminal branches by catching the muscle of the larynx with the tip of the hemostat. A second hemostat then is applied to the lateral vein of the thyroid, which is at the outer surface at the juncture of the middle and lower thirds of the gland. Hertzler<sup>3</sup> has emphasized the importance of this clamp, stating that the cleavage often is lost at this point because of the fact that the fascia planes divide here, one sheath going over the carotid and the other to the gland. Guthrie<sup>3</sup> routinely ligates this vessel first. The third clamp then is applied at the inferior pole. I make it a practice to leave some thyroid tissue at this point, and the clamp is so placed that after it has been applied, it will stand erect in the wound. In my own hands, a great deal of the bleeding which is encountered in thyroid surgery can be lessened if these three pilot clamps are accurately and consecutively applied. The poles and lateral thyroid fascia can then be divided and an incision made along the lateral posterior border at the point at which the gland is to be divided. This incision is carried only for a short distance into the gland—approximately 1 cm. After this has been done, it will be noted that the gland can easily be lifted forward, and at this point the gland then is turned outward, and the dissection carried from the tracheal side. Sistrunk<sup>4</sup> always advocated this procedure, and it has been of great assistance to me. The clamps can then be placed nearly transversely above the trachea into the gland, and the dissection carried from that point outward. In some cases, it may be advisable to split the isthmus first, before starting the dissection on the outside, but ordinarily this is not necessary, and I prefer always to place the pilot clamps and to begin the dissection from the outside of the gland first. In carrying the dissection from the trachea outward, the clamps thus are placed almost transversely, and this eliminates the possibility of having to insert the hemostat downward toward the tracheo-esophageal

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groove, since the transverse application actually is away from the groove. This, of course, is a common site for injury to the recurrent laryngeal nerve.

After the gland has been removed, all ligations are performed with fine catgut ties. I know from actual experience that sewing in the bed

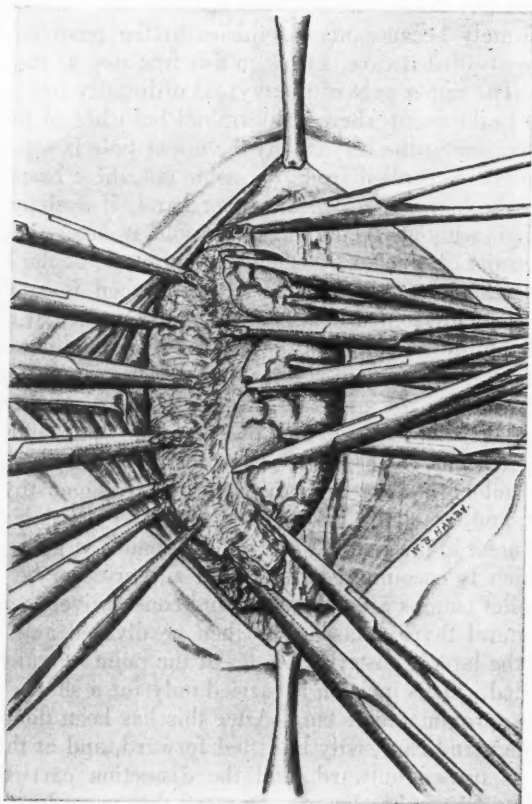


FIGURE 8.—Dissection of gland. After the points within the primary clamps have been divided, the dissection is carried inward from the outside of the gland for about one-third of its extent.

of the gland is a dangerous procedure and if possible, it should not be done. I prefer to ligate the upper pole with catgut suture, inserting it in the same direction as that in which the clamps were applied. After the hemostasis is complete, the same procedure is carried out on the opposite side. There usually is very little difficulty in mobilizing the

# SPECIAL POINTS IN THE TECHNIQUE OF THYROID SURGERY

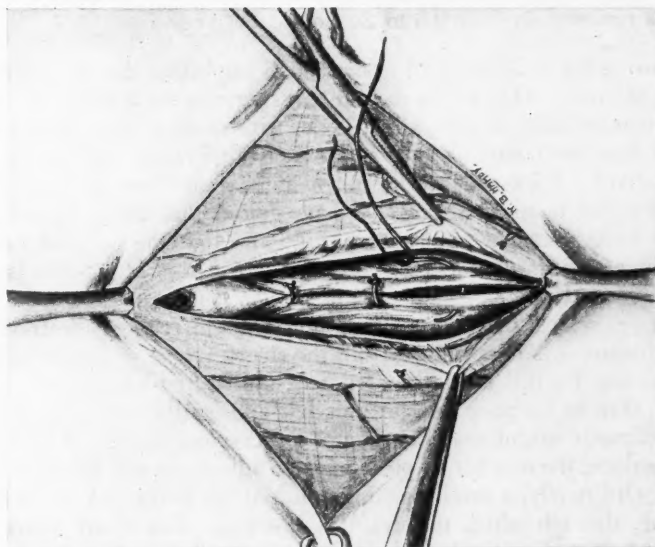


FIGURE 10.—The capsule is closed with interrupted sutures of fine catgut.

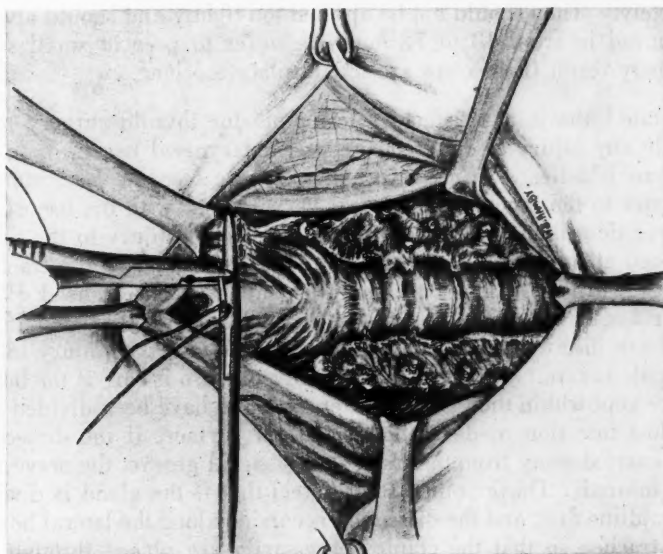


FIGURE 9.—Ligation of the upper pole with double catgut ligature. The pole is lifted up and the ligature always passed from within outward.

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small rubber tissue drain, which is placed beneath the muscles and which is removed in from 18 to 24 hours.

Following thyroidectomy, it is extremely important that an accurate closure be done. One of the most distressing complications is a small adhesion or an adherent scar which moves with swallowing. The patient may, or may not complain of this, but it is always noticed by friends and relatives. I have dissected out a number of these postoperative adhesions and in most instances I have found that the preglandular muscles have retracted from the midline and that the cervical fascia was adherent to the trachea. The correction of this oftentimes is not a simple procedure, because a wide dissection may be necessary before one can again free the preglandular muscles and recover the trachea. In the closure, it is important that all the structures be re-approximated in layers and for this reason interrupted sutures first are placed in the capsule, then in the preglandular muscles, and finally a running suture of fine chromic catgut re-approximates the cervical fascia. I feel that if this is done, the number of postoperative adhesions will be extremely small. Ordinarily, a small opening is left at the lower end of the incision line, through which the drain is inserted. For many years we have used skin clips to close the full thickness flaps. It is important that these clips be placed accurately and at right angles to the incision line. It is a common error to apply these clamps to the side so that they appear at many different angles when the incision line is closed completely. They should not be applied too tightly and should always be removed in from 48 to 72 hours in order to prevent small scars which may result if the clips are left in place too long.

As stated above, a satisfactory technique for thyroid surgery must preclude any injury to either the recurrent laryngeal nerves or to the parathyroid bodies. In my own hands, I have seen the least number of injuries to the recurrent laryngeal nerves occur with the use of the technique described. The most common sites for injury to the nerve have been at the superior pole, the inferior pole, and in the tracheo-esophageal groove at about the middle point between the level of the inferior and superior poles. If the superior pole is free, and if the clamps are inserted from within outward, I believe that injury to the upper pole is rare. Injury at the inferior pole also is rare if the hemostats are kept within the gland. After the poles have been divided and a shallow insertion made along the lateral surface, if the dissection then is carried away from the tracheo-esophageal groove, the nerve will not be injured. On the other hand, I feel that if the gland is divided in the midline first, and the dissection is carried along the lateral border of the trachea so that the clamps necessarily are placed through the tracheo-esophageal groove, many injuries to the nerve will result. In



# SPECIAL POINTS IN THE TECHNIQUE OF THYROID SURGERY

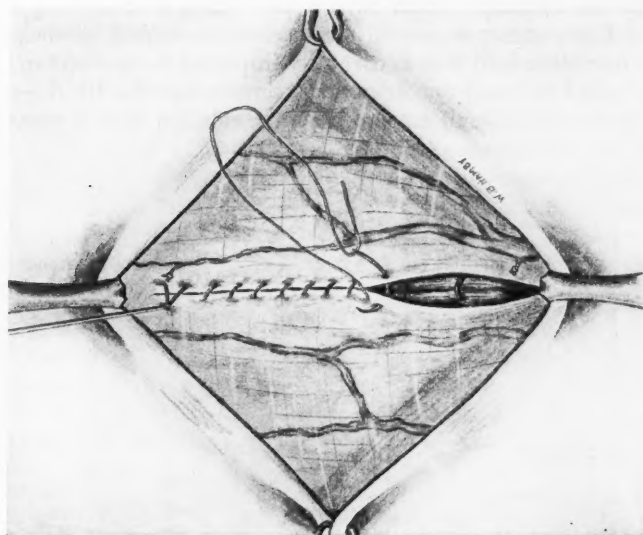


FIGURE 12.—Closure of fascia with fine catgut running suture. A small opening is left in the lower third for drain.

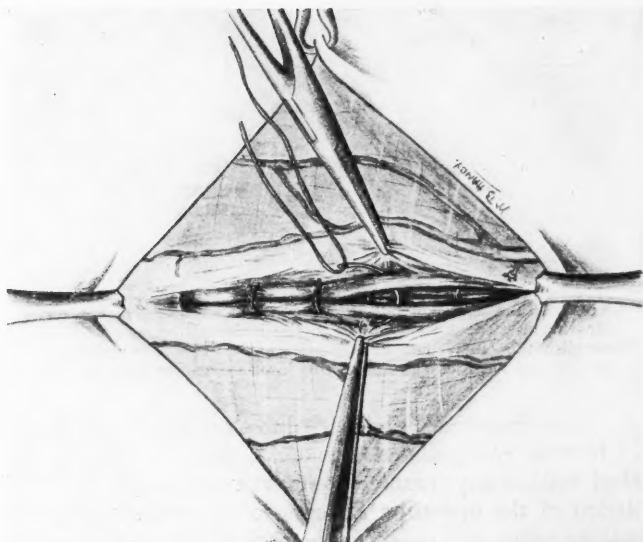


FIGURE 11.—Closure of pre-glandular muscles with interrupted sutures.

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second lobe, inasmuch as the isthmus is divided and the pilot clamps can readily be applied. After such a procedure, a triangular piece of thyroid tissue thus remains in the tracheo-esophageal groove, and the whole operative field then is carefully inspected for oozing, and the patient is asked to cough in order to be certain that the ligatures are securely applied. A small amount of saline solution then is placed in

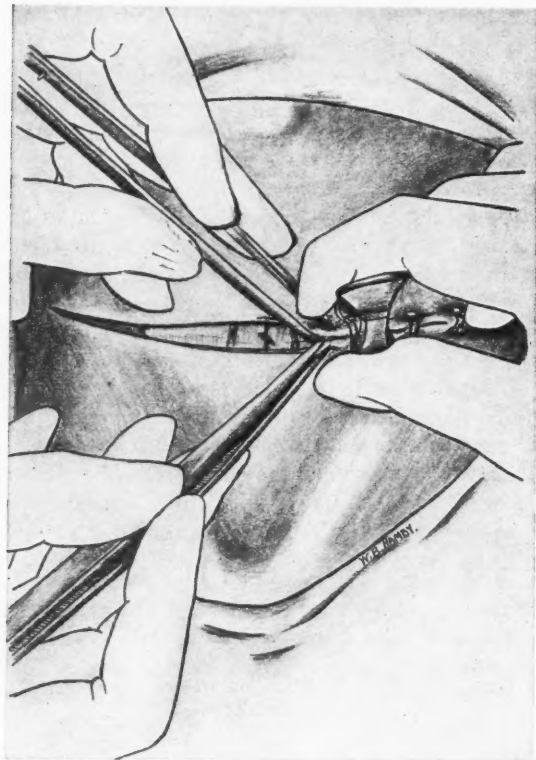


FIGURE 13.—Closure of skin with clips. It is essential that the clips be inserted at right angles to the incision line. To accomplish this, they must be applied from directly above the incision and not from the side as this invariably twists the clip.

the wound. At various times I have tried to close these wounds without drainage. In well encapsulated adenomas, this occasionally can be accomplished without any trouble; however, even though the wound at the completion of the operation appears to be perfectly dry, almost invariably some serum will collect in the neck which must be evacuated. Therefore, it is best to use some type of simple drainage, such as a

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carrying the dissection down along the trachea, there are many small blood vessels which may be in close approximation to the nerve.

I also feel that very few cases of postoperative parathyroid tetany will occur if the capsule is dissected cleanly from the thyroid, care being taken to leave as much of the posterior border of the thyroid as possible. In our own pathological laboratory, Dr. Graham has found from examination of specimens removed at operation, that the most frequent site of removed parathyroid glands is on the lateral inferior border of the gland. Many writers, including Millzner,<sup>5</sup> Lahey,<sup>6</sup> and Terry and Searls<sup>7</sup> have called our attention to the high incidence of parathyroid bodies which lie on the anterior surface of the gland.

The last decade has witnessed a marked reduction in the mortality from thyroid surgery. This is due to the use of Lugol's solution, to more careful and longer preoperative preparation, and to divided operations. Little emphasis has been placed on the morbidity from thyroid surgery, which in most instances can be lessened by a careful and meticulous technique.

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I am indebted to our former Resident in Neurological Surgery, Dr. W. B. Hamby, for the preparation of the illustrations, and to the W. B. Saunders Company, Philadelphia, for permission to reprint them from "Diagnosis and Treatment of Diseases of the Thyroid Gland" by George Crile and Associates, 1932.

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## THE CLASSIFICATION OF ANEMIA\*

RUSSELL L. HADEN, M.D.

### SUMMARY

A laboratory and clinical classification of anemia has been outlined.

The results of the blood study have been correlated with the clinical classification.

The importance of the clinical and hematologic classification in relation to the treatment of anemia has been emphasized and the lines of treatment indicated.

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Changes in the erythrocytes must always occur in anemia since the hemoglobin is constantly decreased. Erythrocytes may be decreased in number, the size may be altered, or the hemoglobin content per cell may vary from normal. No patient with anemia should be treated without a complete laboratory and clinical examination. The blood must be properly studied and classified in the laboratory; the patient must have a careful clinical examination; the results of the laboratory and clinical studies must be correlated. It is my purpose in this paper to describe a method of study of anemia which has proved most valuable in our hands.

No clinical or laboratory classification of anemia suggested in the past has proved satisfactory. Most clinicians have employed only a rough grouping into primary and secondary types. In the primary group have been placed the anemias without apparent cause and those with a color index over 1.00; in the secondary group, those with known cause, and those with a color index less than 1.00. Such a classification confuses clinical and hematological data and is not really workable.

In every animal the blood is undergoing constantly a rapid ebb and flow. Erythrocytes and hemoglobin are always being formed and destroyed. The life span of the erythrocyte of man is about four weeks, which means that every month the entire store of circulating and reserved red cells is replaced. An anemia is simply a loss of balance between this normal process of destruction and replacement. In every anemia it is necessary to know:

1. How many cells and how much hemoglobin have been lost.
2. What qualitative changes, such as variation in size and hemoglobin content of the cells, have taken place.
3. How rapidly the cells are being destroyed.
4. How rapidly the cells and hemoglobin are being replaced.

\*Reprinted by permission from the Journal of the Medical Society of New Jersey, 31:511-514, September, 1934.

## THE CLASSIFICATION OF ANEMIA

This information can be easily obtained by a systematic blood study. A red cell count is done, the hemoglobin is determined in grams per hundred cubic centimeters, and the volume of packed cells per hundred cubic centimeters of blood is measured by centrifugalization of 10 c.c. of blood containing an isotonic anticoagulant. From these data the volume and hemoglobin content of the mean cell can be calculated and also the amount of hemoglobin per unit volume of cell relative to normal. The best index of the rapidity of the blood destruction other than the red cell count is the amount of bile pigment in the blood, provided there is no obstruction of the biliary tract. The activity of red cell formation in the marrow is best determined from the level of reticulocytes in the circulation since these are young cells. (For the technical details of such a blood examination, see the author's paper "The Technique of a Blood Examination," Jour. Lab. & Clin. Med., 17:843-859, 1932.)

The primary classification of anemia from a laboratory standpoint is based on the volume and hemoglobin content of the mean red cell. Only six groupings are possible.

1. *Normocytic and normochromic.* Here the volume and color indices are within normal limits (0.90 to 1.10). It is apparent that the number of cells must be reduced if anemia is present.

2. *Macrocytic and hyperchromic.* In this type the mean cell is larger and contains more hemoglobin than normal so both the volume and color indices are greater than 1.00. Since the amount of hemoglobin per cell is increased, the number of cells is always decreased.

3. *Macrocytic and normochromic.* The cells are large but the mean amount of hemoglobin per cell is normal; the volume index is greater than 1.00; the color index is within normal limits.

4. *Macrocytic and hypochromic.* Here the volume index is still increased, but the color index is below normal.

5. *Normocytic and hypochromic.* The mean cell volume and the volume index are within normal limits but the hemoglobin per cell is decreased as shown by a color index of less than 1.00.

6. *Microcytic and hypochromic.* The volume index is below the lower limit of normal (0.90). The hemoglobin per cell in such a case is necessarily less than normal so the color index is low. Usually the number of red cells shows little if any decrease.

To complete the laboratory study the pigments in the plasma are measured by comparison with a dilute solution of potassium bichromate and recorded as the icterus index or determined quantitatively by the van den Bergh method. A vital stain is made and the reticu-

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locytes counted; a film stained by Wright's stain is examined for variations in diameter and shape, basophilia, nucleated erythrocytes, relative number of platelets and a differential count of the leucocytes.

The laboratory classification of anemia is thus simply a descriptive one. An etiologic classification is always the most desirable one, and such a classification may be made from the clinical standpoint. A satisfactory clinical grouping based on method of production is shown in Table I.

TABLE I.

CLINICAL CLASSIFICATION OF ANEMIA BASED ON METHOD OF PRODUCTION

- I. Increased Blood Loss
  - a. Mechanical from acute hemorrhage as in:
    - 1. Trauma
    - 2. Peptic ulcer
    - 3. Uterine bleeding
    - 4. Disturbance in blood coagulation
  - b. Accelerated destruction as in:
    - 1. Chronic hemolytic icterus
    - 2. Hemolytic anemia due to infections and poisons
- II. Decreased Blood Formation
  - a. Depression of marrow function in:
    - 1. Idiopathic aplastic anemia
    - 2. Cachexia, chronic intoxication, metabolic disturbances, poisons, radioactive substances, malignancy or infiltration of marrow by tumor or leukemia.
  - b. Deficiency in specific substances necessary for normal red cell formation as:
    - 1. Deficiency in specific anti-anemic factor of liver leading to pernicious and other macrocytic anemias.
    - 2. Deficiency in iron and perhaps other unknown substances necessary for hemoglobin formation as in chronic hemorrhage, dietary deficiency in iron, and disturbance in absorption or assimilation of iron (idiopathic, hypochromic and microcytic anemia).

The laboratory and clinical findings may be correlated and in some instances the laboratory findings indicate the etiology of an anemia from a clinical standpoint. If the anemia is caused by an acute mechanical loss of blood, the cells remaining are normal in size and hemoglobin content, and the volume and color indices are normal. The anemia is normocytic and normochromic. The bile pigments in the plasma are decreased and the reticulocytes are increased if the bone marrow responds normally. With increased hemolysis the bile pigments are markedly increased, so the icterus index is high. The



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reticulocytes are usually much increased in a chronic hemolytic anemia since the bone marrow is overactive in an attempt to compensate for the increased blood loss. The volume and hemoglobin content of the mean cell show little change.

In the large group of anemias due to a simple quantitative defect in delivery of the red cells from the marrow, such cells as are formed are normal in size and hemoglobin content. The volume and color indices are normal. Not infrequently, however, the anemia resulting from malignancy, toxemia, infection, and other causes is not simply a quantitative deficiency, but is qualitative also, since the primary disease interferes with the absorption or utilization of the substances necessary for the normal formation of blood. Here the blood findings are a combination of those characteristic of a quantitative and a qualitative deficiency.

The qualitative deficiencies show characteristic findings. With a deficiency in the specific anti-anemic factor of liver, the red cells in the circulating blood are larger than normal, so the volume index is increased. This specific principle is necessary for the normal growth from the megaloblast stage. Megaloblasts are large cells; hence the macrocytosis since maturation is not normal. The bone marrow is red because it is overactive. Many cells die in the marrow because of their inability to mature and thus increase the bile pigments in the plasma. The reticulocyte count is low. With a deficiency in iron, the cells are small and deficient in hemoglobin although the total red cell count is decreased little if at all. Hypochromia as evidenced by a low color index is the first abnormality to develop if the supply of iron is inadequate. If the hypochromia continues, the cells decrease in size and the volume index falls, probably because there is no need for a normal cell mass, since there is no hemoglobin to fill it. The formation of bile pigment is at a low level because less hemoglobin is destroyed and hence the icterus index is decreased. The reticulocyte count is variable but never high.

Not infrequently more than one factor is operative in the causation of an anemia, and so the laboratory findings represent a summation of those characteristics for the different types of anemia. If there is a deficiency in both iron and the anti-anemic factor of liver, the macrocytosis and hyperchromia due to the lack of the anti-anemic factor of liver may be neutralized by the microcytosis and hypochromia of the iron deficiency. The cell size and hemoglobin content may then be within normal limits. Malignant disease may depress the marrow, interfere with the utilization of a specific factor, and also cause hemorrhage. In such a case, there are three factors in the causation of the anemia.

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### DISCUSSION

With the laboratory and clinical study here outlined a satisfactory classification of almost every anemia can be made, and the proper treatment administered. The classification is more difficult in cases in which more than one factor is operative. It is increasingly evident in the study of anemia that the utilization of a specific factor may be interfered with even when the supply is adequate. Infection often prevents the normal utilization of specific factors. Thus it is well recognized that if an infection develops in a patient with pernicious anemia, the intake of liver or liver substitute must be increased. This fact indicates that the infection interferes with the absorption or utilization of the specific and anti-anemic principle.

It is apparent that the proper treatment is usually indicated if the study is complete. In the specific deficiency anemias the adequacy of treatment must be determined from the laboratory study of the patient's blood. No patient with pernicious anemia is adequately treated if a macrocytosis of the erythrocytes persists, and so the aim of treatment should be to obtain a normal color and volume index. Likewise in a case of iron deficiency anemia, if enough iron be given and if utilization is normal, the cells become larger and filled with hemoglobin, and the color and volume index return to normal.

## DISCUSSION OF HEADACHE\*

### HEADACHE OF GASTRO-INTESTINAL ORIGIN

C. L. HARTSOCK, M.D.

That most troublesome symptom, headache, so frequently is associated with disorders of the digestive system—especially nausea, vomiting, and constipation—that a cause and effect relationship certainly would appear to exist. When these two symptoms coexist in the same individual, usually the physician or possibly the more specialized gastro-enterologist is consulted in an effort to discover what is wrong with the digestive system, because the majority of patients believe that this disturbance of the digestive tract is the cause of the headache. While some headaches undoubtedly are due to faulty elimination habits, more often than not, the cause of these coexisting symptoms lies outside the gastro-intestinal tract. No matter whom such a patient consults, a very difficult diagnostic and therapeutic problem presents itself.

I have been accustomed to think of such problems as having three possible solutions. First, the disease may be primary in the central nervous system with secondary gastro-intestinal symptoms; second, the disease may be entirely outside either domain with the production of reflex symptoms in both; or third, the headache may be of gastro-intestinal origin, and this is placed last in my classification, because if a careful search is made, the cause of most headaches usually will be found outside the gastro-intestinal tract.

The specialist in any field, and this applies also to the gastro-enterologist, is prone to view all human ills from his narrow viewpoint, and unless he thinks of other possibilities first, often he will miss the true solution of a problem. Therefore, I never approach the problem of the origin of headache with the idea that it is secondary to some gastro-intestinal condition. An extremely careful examination of these patients is necessary to view the situation in the right perspective. Studies of the gastro-intestinal tract should be deferred until other examinations have been completed and other more specific causes ruled out. A minimum routine neurologic study should include a study of the fundus for evidence of increased intracranial pressure or vascular changes, a study of the pupillary reactions, the reflex actions, station and gait. These examinations often will give the leading clue that will suggest the need for further examinations as, for instance, of the visual fields, or of the spinal fluid, a roentgenogram of the skull or an encephalogram.

The level of the blood pressure, the cardiovascular findings, the number of blood cells, the results of the blood Wassermann test and of

\*Presented at a Wednesday Evening Staff Meeting.

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the examination of the urine may give clues as to the origin of the headache and digestive upsets. If the cause of headache is not determined early in the examination, a careful refraction of the eyes should be made, which should include also a measurement of the ocular muscle coordination. Examination of the eyes alone frequently will explain both the headaches and digestive symptoms.

A careful inquiry should be made in regard to manifestations of allergy in the patient and in his family, and if the slightest clue of the presence of allergy is found, it is advisable that a thorough study be made from this standpoint. Probably more coexisting headaches and gastro-intestinal symptoms will be found to be due to this cause than to any other single cause.

If the presence of brain tumors, infections of the central nervous system, cerebral arteriosclerosis, refractive and muscle errors of the eye, hypertension, uremia, cardiac decompensation, allergy, lead poisoning, hypothyroidism, and syphilis as causes of headache associated with gastro-intestinal symptoms are ruled out, then attention should be directed to the gastro-intestinal tract. The functional disturbances rather than the organic diseases of the gastro-intestinal tract are by far the more common causes of headache. Rarely is a headache cured by the removal of a diseased gallbladder or appendix or by an operation for a gynecological condition. Of course, no criticism is made of the performance of these operations for the relief of the definite pathological local conditions, but when the major symptom is headache and the gastro-intestinal disturbance is of less importance in the patient's mind, then one should be very careful about the prognosis in regard to the headache. One should also be doubly certain about the correctness of the diagnosis of abdominal disease before operation is performed because certain functional headaches, and especially migraine, mimic gastro-intestinal disease, and also draw undue attention to the pelvis because of their frequent occurrence at or near the time of the menses. Unless pelvic and abdominal operations are performed when the patient is near the climacteric, at which time migraine headaches naturally tend to disappear, the patient rarely is benefited except for a short period of time which is due to the rest after the operation.

Three types of headache are at least partly related to the gastro-intestinal tract, and in the presence of these, the gastro-intestinal tract should be studied thoroughly to aid in the treatment of the headache. Probably the most common type of headache is that seen in a very large group of patients who complain that a headache is associated with constipation. Some of these patients insist that if a bowel movement does not occur every 24 hours, a headache results. Such patients usually are slaves to the cathartic or enema habit. The cause of such head-

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aches is not very well understood, but usually it is ascribed to auto-intoxication which in itself means little or nothing. A more satisfactory explanation is that the patient is allergic to the end product of digestion or more likely to the bacterial flora of the intestinal tract, especially the colon bacillus. The absorption of the chemical products of putrefaction and fermentation must also be considered. It is possible that the headache is only a part of the same functional neurogenic disturbance that causes the constipation. The only pathology which is found in such cases is usually in the colon, which is irritable but may be of the spastic or atonic redundant type. The great majority of cases will gain relief by the simple bowel management of securing natural elimination without catharsis or enemata. Autogenous vaccines of colon bacillus should be used in the more obstinate cases if intradermal tests show that the patient is sensitive to this allergen. This type of headache occurs very commonly, it is the cause of much semi-invalidism, and it merits the careful attention of the gastro-enterologist.

Another type of headache in which the gastro-enterologist can be of great assistance occurs in those individuals who have a poor constitution, who are chronically tired, and who usually complain of a great deal of indigestion. The headache in these cases probably is not caused directly by the indigestion, but rather by fatigue. Very little relief, however, is obtained by treatment unless the patient's general condition is improved, and this rarely occurs unless the digestive symptoms are adequately treated. A high vitamin, high caloric diet with frequent small feedings, regulation of the bowels, adequate rest, mild and limited exercise, physiotherapy, sedatives and psychotherapy usually will correct the digestive disturbances, add weight and strength, and with the improved general condition, the headaches will disappear.

The third type of headache in which the gastro-enterologist should interest himself is migraine—the cause of which is unknown. It certainly is not due to disease of the gastro-intestinal tract, and it has been mentioned that abdominal operations do not cure it. Why then, should the gastro-enterologist study this condition so carefully? In the first place, the nausea and vomiting which in many cases accompany migraine are so much more distressing to the patients than the headache that they seek relief primarily from this condition. The patients are convinced that the primary trouble is in the gastro-intestinal tract, and because they vomit bile toward the end of the attack, they believe they have liver or gall bladder trouble, and consequently, they easily become the innocent victims of useless operations upon the gall bladder. One purpose of an adequate gastro-intestinal study is to convince the patient of the real nature of his trouble.

Certain headaches which simulate migraine very closely are due to partial obstruction high in the intestine, especially if associated with

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duodenal stasis. This cause for headache can be found by adequate study, and the condition can be relieved by appropriate treatment. Such patients usually have an accompanying alkalosis.

Another reason for study is that the vomiting of migraine seems undoubtedly to be due to a functional reverse peristalsis of the upper intestinal tract. If no contraindications exist, such as an irritable colon, the occasional calomel and saline purge appear to lessen the frequency of such attacks. Duodenal lavage will give the same results. Undoubtedly the general treatment of the patient which includes dietary and bowel management, especially in patients who are high strung and who have irritable colons, gives good results.

The gastro-enterologist should also be interested in manifestation of food allergy which in some cases of migraine appears to be the sole etiological factor. Migraine appears to be a disease of the nervous system which is set off in explosive attacks by trigger points, and the complete general examination of the migraine sufferer should never be neglected, but for the above-mentioned reasons, the gastro-enterologist should take a very active interest in these patients.

Patients frequently ascribe their headache to such factors as nervousness, omission of food for more than the usual time, omission of the habitual morning cup of coffee, the ingestion of certain foods or combinations of foods, and numerous other idiosyncrasies, but with the possible exception of allergy and hypoglycemia, these headaches do not appear to be due to any detectable functional or organic disturbance of the gastro-intestinal tract, and they should be treated symptomatically and empirically.

In conclusion, the only headaches that appear to be due directly to pathology in the gastro-intestinal tract are those which are due to chronic constipation, either from absorption of toxic products or from sensitization to intestinal contents, and those due to alkalosis of high intestinal obstruction. Other headaches are caused by an outside factor with associated digestive symptoms, the relief of which will do much toward clearing up the headache.

Still other headaches associated with digestive symptoms are caused by some specific pathology outside the gastro-intestinal tract. This must be discovered and treated before either the headache or the digestive symptoms will be relieved.



## HEADACHE OF RENAL ORIGIN

R. H. McDONALD, M.D.

Headache of renal origin is associated with toxic absorption from an inflamed kidney, it is secondary to an accumulation of waste products due to renal failure, or it may be the result of mechanical changes in circulation following a renal lesion. At some time during the course of disease of the kidney, headache was an outstanding symptom in approximately one-third of our cases.

In acute hemorrhagic Bright's disease, headache commonly accompanies the fever, as is true in the presence of fever from any cause. In this instance, it probably is caused by meningeal irritation which is a result of the toxic products of disturbed metabolic processes. Such headache usually is generalized and dull. In severe cases where marked elevation of blood pressure accompanies the renal lesion, severe throbbing headache may result from increased pressure within the cranium which accompanies the general increase in arterial tension. Such headache may be localized, and it may be increased by effort or a dependent position of the head. Occasionally headache in the presence of acute nephritis is the result of secondary anemia and consequent inanition of the brain, although in the initial stages of renal disease, anemia seldom advances to a stage in which this occurs.

In the active, chronic and terminal phases of hemorrhagic Bright's disease, headache is a common finding and may be one of the early symptoms which induces the patient to consult his physician. In these patients, it may be accompanied by vertigo, anorexia, nocturia, polyuria, edema of the extremities and general weakness. It may be the result of meningeal irritation from the end products of nitrogen metabolism, or it may be related to pressure changes within the cranium as a result of general vascular disturbances. Occasionally, it is the result of cerebral inanition secondary to the marked anemia which frequently is present in these cases. In patients who have chronic nephritis, headaches usually are generalized and lack the localization of the commoner forms of reflex headache. Occasionally in chronic nephritis, it is possible that the retinal inflammation which occurs is in itself a cause of headache of ocular origin.

With the onset of uremia in terminal Bright's disease, headache is a very frequent and often an initial symptom. It may occur in any part of the head—frontal or occipital, or it may be hemicranial, in which case, it simulates migraine. This is especially true since it frequently is accompanied by nausea and vomiting. As a rule, headache in the presence of uremia is not severe in contrast to that observed in the hypertensive encephalopathy to be discussed. Volhard does not regard

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headache as a true symptom of uremia, but it has been noted repeatedly that patients who have not had headache previously, do have it as an accompaniment of the abnormal increase of non-protein nitrogen in the blood which is significant of the uremic state.

Headache is a symptom from which almost all patients with essential hypertension suffer at some time, and frequently it is an initial symptom. In fact, it is common to find that patients with essential hypertension have suffered since childhood from headaches which frequently are of the type suggestive of migraine. Evidently such a history indicates some inherent instability of the autonomic nervous system and of vasomotor control which later renders these patients susceptible to essential hypertension. The headaches of hypertensive encephalopathy may be generalized or localized in the occipital or frontal areas; occasionally, they are hemicranial. They may be preceded by visual or auditory aura, and at times they may be accompanied by nausea and vomiting. The headache may vary from a dull area or feeling of increased pressure in the cranium to the most severe type of intense throbbing which is coincident with the heart beat. Janeway describes the typical headache of hypertension as one which awakens the patient prematurely, attains its maximum intensity before breakfast, and disappears during the course of the morning. However in many patients, this is reversed and the maximum pain is attained with the increased mental or physical effort of the day which is associated with consequent effect upon the level of blood pressure.

The reason for the frequent occurrence of headache associated with hypertension is not entirely clear. It is known that the intracranial pressure, as revealed by lumbar puncture, does not vary absolutely with the arterial tension, although it tends to follow in the same direction, and frequently a lumbar puncture relieves much of the headache. There is no necessary parallelism between the height of the blood pressure and the liability to headache. Some patients with severe hypertension never have headaches; therefore, it is apparent that some factor other than mere mechanical elevation of pressure is present. Post-mortem findings suggest that the majority of patients with essential hypertension have well-marked cerebral arteriosclerosis, even though they showed no definite evidence of cerebral disease during life, and it therefore is likely that sclerotic vascular changes and disturbances of cerebral or meningeal circulation are responsible for the symptom. The sudden appearance and disappearance of the headache in some cases would suggest that vasoconstriction of the sclerotic vessels may be a factor, possibly by the initiation of some degree of cerebral anemia. Sudden rises in pressure are apt to be accompanied by violent headache. Of course, renal insufficiency in essential hypertension may be accom-

### HEADACHE OF RENAL ORIGIN

panied by uremic headache, but the vast majority of headaches of patients with essential hypertension are due not to uremia as is indicated by the normal blood findings.

The sequelae of essential hypertension may be the cause of severe headache. The onset of a cerebral hemorrhage may be marked by an uncontrollable localized pain in the head which apparently is the result of meningeal irritation and cerebral damage. Cerebral thrombosis may produce similar symptoms. Occasionally, in hypertensive encephalopathy, edema of the brain develops, and intracranial pressure is increased to such an extent that choked disc appears. In such cases, the clinical picture of violent headache, nausea, vomiting, convulsions and marked elevation of cerebrospinal fluid pressure appears as in any other space-filling lesion of the cranium.

Recognition of the renal origin of the symptom is dependent upon the history of antecedent renal disease or hypertension, urinary examination, renal function and blood chemistry studies. Apart from the use of sedatives and analgesic drugs for symptomatic relief or the judicious use of lumbar punctures in a few cases, treatment must be directed toward the care of the underlying renal condition.

## HEADACHE OF OCULAR ORIGIN

A. D. RUEDEMANN, M.D.

Headaches frequently are of ocular origin, and the fact that the eyes are used from 12 to 15 hours every day makes it important that, irrespective of the location of head pain or of its severity, the eyes should be examined by a competent oculist.

Very often the patients themselves are largely responsible for the incorrect diagnosis of many headaches of ocular origin. Most people do not like to wear glasses and because of the fear that they may be found necessary, important facts concerning the history of the headaches are withheld and certain symptoms which are not referable to the eyes may be emphasized in order that glasses will not be recommended. Therefore, a complete history should be elicited, and a very thorough examination should be made.

Headaches due to disturbances of the eye usually are bilateral; however, a sufficient number of unilateral headaches and pain are of eye origin that they too must be discussed.

The most important and the most severe of the unilateral causes is local inflammation which includes such conditions as iritis, iridocyclitis, choroiditis of inflammatory origin, and acute or inflammatory glaucoma. Evidence of these conditions not always is apparent, but the pain produced is severe, stabbing and boring in character. It radiates deeply through the orbit, over the side of the head, and down the neck into the shoulder. When such pain is present, the attention of an experienced oculist is required.

Spasms of the ciliary muscle may occur following thyroidectomy, during transitory hypothyroidism, ordinary hypothyroidism, or they may accompany parathyroid tetany. The pain produced by this condition is severe in character, of short duration, but of terrific intensity. Sudden blurring of images and soreness of the eye mark the onset of this disease and here again, a thorough examination of the eye should be made which should include a search for a refractive error, for evidence of parathyroid tetany, or a low basal metabolic rate.

Supra- and infraorbital neuralgia is another form of headache which requires a differential diagnosis. This neuralgia may be associated with a glaucoma or it may simulate in type and duration the pain that accompanies glaucoma. However, in the presence of glaucoma, the eyeball is found to be more red and hard. The pain is constant instead of stabbing, and there is vision loss.

Errors in refraction are by far the most frequent source of headache of ocular origin. The most common of these errors of refraction is hyperopia which may or may not be accompanied by astigmatism. Two

## HEADACHE OF OCULAR ORIGIN

of the most important of the many factors which cause headache due to farsightedness are the constant effort of accommodation or just looking and the inability of the eyes to adjust to the inequalities in amount of hyperopia which usually exist in these cases. If astigmatism is associated with hyperopia, another factor is added to the production of pain. This pain is frontal or bitemporal, or it may be more noticeable on one side than on the other. Before treatment is prescribed for these patients, the occupation and the mode of living must be known, as well as the reading ability and use of light. Then a well-fitted pair of lens may be prescribed, which should be checked from time to time. This should be done after the use of homatropine or even atropine in testing the more severe forms and also in the younger patients. These glasses should be worn as a therapeutic measure, although, in some instances, it is necessary that they be worn only for reading. In some cases of hyperopia, the vision is cut down at first until the amount of relaxation of the ciliary muscle is equal to the amount prescribed in the lens in order that the effort of accommodation may be relieved. In such instances, considerable persuasion sometimes is necessary to convince a patient that the glasses are of benefit and that they must be worn for some time before the maximum benefit may be derived from their use. Each case must be considered as an individual problem, and it should be remembered that in the presence of hyperopia, no glasses should be discarded until they have been worn constantly for six months in order to determine accurately whether relief from symptoms may be gained from their use.

Patients with myopia usually do not complain of headache, but it may be present in some cases of nearsightedness where the eye is sensitive to light or where an inequality of the refractive error causes trouble. In other instances, the pain may be supraorbital or bitemporal, but ocular pain is not a common finding. A well fitted pair of glasses produces a happy patient who is able to see well. No medical prescription equals the return that a pair of such lenses gives in sight and happiness to the patient who has myopia.

Mixed and other errors of astigmatism such as corneal scarring, conical cornea and certain minor lesions produce pain. Although patients with these conditions wear glasses, they still are not always made comfortable, and even though the condition may be improved, it is not always wholly corrected. Constant ocular attention is required, and some patients never are relieved completely from their headache. Corneal lesions frequently change their shape and change the axis of the astigmatism.

No single phase of refraction is more important than is the treatment of muscle errors. The minor causes are glasses improperly fitted to

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the face of the patient, tilted lens, too wide lens, frames which are off center or rotated in round frames, and rarely, eyes which are uneven in position, that is vertically, or the distance from center of nose is unequal.

Mild muscle errors present a serious problem, and they are disturbing to the patient's comfort, whereas the more severe errors, such as paralysis, may be insignificant so far as symptoms are concerned. In many cases, both the student who suffers from a nervous breakdown and the executive who is not able to concentrate are having trouble with their eyes.

Pain due to muscular instability or weakness is very common, and no relief can be secured unless the condition is corrected. Many factors aid in the production of muscle imbalance—general diseases such as hyper- or hypothyroidism, parathyroid tetany, Parkinson's disease, encephalitis, diabetes, allergy, or any severe debilitating state. An ocular muscle error may be constant or inconstant, mild or severe, but all are annoying to the patient and may lead to total incapacitation and a serious mental condition.

In the presence of muscle imbalance, the head pain is in the post-occipital or suboccipital region, or it may occur at the tip of the mastoid bones where the sterno-cleido-mastoid muscles are attached; usually however, it is suboccipital where the neck muscles are attached along the superior and inferior nuchal lines. This is due to the fact that the patient, in an effort to overcome the eye strain due to muscle imbalance, assumes certain positions of the head which in turn, produce cramps in the muscles of the neck or pain near the mastoid. Both glasses and muscle exercises may be prescribed in these cases and still the muscle error may remain uncorrected. In such cases, medical attention is required which is accompanied by treatment of the ocular muscle. Eye muscle surgery, either advancement or recession, is indicated in a number of cases where the error is too great to be corrected by exercise. There are no more grateful patients than those who are relieved from the pain caused by muscle errors, because in many of these cases, a diagnosis has been made of cervical arthritis and treatment for such a condition has been carried on for some time.

Occasionally, terrific headaches which are so severe that the patient is kept awake at night and which are accompanied by nausea and vomiting are thought to be symptoms of cerebellar tumors or abscesses. Careful examination often shows that such headaches are the result of only slight muscle error plus hyperopia, and this emphasizes the importance of a careful ophthalmological examination before any radical procedure is undertaken for the relief of a suspected cerebellar tumor in such circumstances.



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It cannot be emphasized too strongly that a thorough examination of the eyes should be made in every case of headache, and if the headache is found to be of ocular origin, correct glasses or exercises should be prescribed. It must be remembered also that because a patient wears a pair of glasses, this does not prove that the eyes have been examined properly or that the disease which causes the condition has been corrected. In some cases, glasses may be worn a long time before new correction is necessary, while other patients require constant attention. The patient who has changed his occupation recently and sometimes the individual with what seems an insignificant position often are subjected to unusual eye effort. It should be remembered that glasses are much better for the patient than the numerous headache tablets and further, that the latter never correct the cause.

The decision whether glasses should be prescribed and worn is one for the oculist, and not one for the patient or the patient's parents, and they should not be cast aside indifferently by a medical man to appease a hypersensitive patient. The fact remains that until the cause is corrected properly, the head pain will persist.

## HEADACHE OF NASAL ORIGIN

W. LORNE DEETON, M.D.

The majority of patients in their quest for relief from headache consult a rhinologist at some stage of their illness. It has been found that a large proportion of these patients believe they have sinus trouble, and in many instances, they have been advised by even their own doctor that their headache is due to a sinus infection.

Two very definite statements may be made in regard to headache of nasal origin—first, the sinuses and upper respiratory tract are not a frequent cause, and second, headache is not one of the outstanding symptoms of sinus disease. Years ago, Gruenwald of Vienna taught that headache was present in one hundred per cent of the cases of acute sinus disease and in fifty per cent of the chronic cases. A recent analysis of a series of new cases seen in the nose and throat department of the Cleveland Clinic revealed that headache was a symptom in only twenty-seven of two hundred ninety-five consecutive cases of sinus infection, and of these, twenty-five were acute cases. Therefore, of two hundred and seventy cases of chronic sinusitis, pain, or headache was the chief complaint in only two cases—less than one per cent. This great change in statistics is due to a more thorough search for the cause of the headache and to better diagnoses.

By far the most common symptom of sinus disease is a post-nasal discharge. This was the chief symptom in eighty cases. Other symptoms in order of their frequency were nasal discharge, recurring head colds, nasal obstruction, ear complaints, cough with and without the production of sputum, asthma, and allergy. In this group of patients, twenty complained only of cough or bronchitis. Very often a patient comes to us after a diagnosis of frontal sinusitis has been made because of pain over the frontal region. Of twenty-five cases of acute maxillary sinusitis, pain was present over the affected cheek in nine instances and over the eye in four. In one case, the pain was referred over the opposite antrum which was quite clear on transillumination.

One of the most important causes for pain and headache of nasal origin is a high deviation of the nasal septum which crowds against the middle turbinated bone and creates pressure on certain nerves. Other causes are enlargement of a turbinate, such as is produced by a cystic degeneration of the middle turbinated bone, swelling of the polypoid sinus mucosa which causes pressure within the sinus, stasis following obstruction to drainage, ulceration of the sinus mucosa, and an active congestion of the cranial circulation which can be activated greatly by the use of alcohol or tobacco. In one case which we saw, a large cyst in an antrum caused pressure and pain, and its removal relieved the

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headache. The usual clear, yellowish fluid which contained cholesterol crystals was found in this cyst.

Some of the complications of sinus disease produce headache. Meningitis causes a headache of distressing severity. In the presence of brain abscess, which is not a common complication, headache may be an early symptom which is associated with vomiting, choked discs, constipation, subnormal temperature, and a slow pulse. All these symptoms may not be present, but headache usually is found in conjunction with two or three of the other symptoms mentioned. In the presence of brain abscess of sinus origin, the headache usually occurs in the frontal region. It is dull and heavy, and sometimes it is excruciating in severity. Even when the abscess is in the frontal lobe, the headache may be occipital or parietal.

No great microscopic search is necessary to detect the sinus infection that may be responsible for headache. A carefully elicited history, the clinical findings, transillumination, roentgenograms, and the location of pus will all help, but of these, a good history is by far the most important.

Acute osteomyelitis of the frontal bone will produce severe pain and headache even though there is pus within the frontal sinus which a roentgenogram may not reveal within the first week; however, edema invariably will occur over the sinus. In cases of chronic sinusitis, a good roentgenographic study usually gives sufficient information for diagnosis without the injection of lipiodol. We find that the use of lipiodol in the sinus is of more importance in the demonstration of an entirely clear sinus than in the demonstration of the presence of disease.

Some of the more common factors that produce headache or pain which often are confused with sinus infection are eye strain, eye muscle error, migraine, fifth nerve neuralgia, syphilis, dental infection, an impacted third molar, and pain in the occipital region which runs down the back of the neck. The latter often is associated with high blood pressure, but frequently it is mistaken for infection in the sphenoid sinus. With the cooperation of a competent allergist, many headaches which have been attributed to hyperplastic ethmoiditis and sphenoiditis will be found to be due to allergy. With the aid of the allergist, we have also been able to relieve several patients from their "migraine" headaches which had been present for years. One patient has been completely free from headaches for sixteen months since wheat was eliminated from his diet.

Occasionally, we have a patient who believes that he has sinus or mastoid infection because of atypical pains in these regions. In many instances, examination reveals a low basal metabolic rate, secondary

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anemia or a combination of both, and treatment directed toward these conditions usually relieves the headache.

Three cases which were seen recently will illustrate some of the points which have been mentioned.

*Case 1:* The patient was a woman who had pain and headache over the left brow which had been present for two weeks. Her physician felt that infection was present in the antrum, so it was punctured and washed out. According to the patient, no pus was found, but the pain persisted, and the puncture was repeated, still with no relief from pain. After the third puncture, the patient noticed that she had double vision, and when she looked into the mirror, she saw that her eye on the affected side would not turn. It was found that this patient had a paralysis of the sixth nerve. Had a little time been spent in taking this patient's history, the fact would have been elicited that she had had several miscarriages, and that serological study was indicated. The blood Wassermann test gave a four plus result and this revealed the cause for the headache.

*Case 2:* The second patient was a woman who had been advised two weeks previous to our examination to have an operation for the relief of headache over the right brow. No evidence of sinus infection could be found either by clinical examination or by x-ray. The patient was sent to the eye department and she reported that from the time drops were put in her eyes, and dark glasses had been worn, complete cessation of the headache occurred.

*Case 3:* The third patient was a woman who was examined first in 1929. Her complaint then was of pain over the right side of the face. The history notes made at that time stated that sinus infection was not the cause of the pain. She was not satisfied and went to another doctor who performed an operation on the right antrum. The pain persisted, and it was felt that it must be due to infected teeth. Therefore, four teeth were extracted, and if one can believe the patient's statement, each was a vital tooth. Still the pain persisted and the patient returned here again. Examination revealed that the pain was due to fifth nerve neuralgia and could be relieved only by measures directed toward that condition.

## HEADACHE OF NEUROLOGICAL ORIGIN

A. T. BUNTS, M.D.

The frequent occurrence of headache which is a presenting symptom and often of a disabling nature makes it of great importance for the physician to identify the underlying cause. Too often, headache is treated symptomatically in the presence of unrecognized grave organic disease. The experimental approach to the study of headache has been difficult because of the absence of objectivity of the symptom and the inability of animals to make us acquainted with the exact nature of their sensations.

Elsberg and Southerland,<sup>1</sup> in their studies on headache, state that sensory impulses may originate within the cranial cavity, or the primary receptors may be outside the cranial cavity. Pathways must consist of (1) afferent tracts from receptors, (2) a central station, and (3) pathways of pain to the cortex and consciousness.

Afferent impulses must travel along either somatic or sympathetic nerves. The nerves supplying the dura and its vessels are derived chiefly from the trigeminal nerve, the vagus nerve, and the sympathetic system. The dura of the anterior fossa of the skull and the falx cerebri are supplied by branches of the first and second divisions of the trigeminal nerve. The dura of the middle fossa is supplied by the third division of the trigeminal nerve, and the dura of the posterior fossa and the tentorium are supplied by the first and second divisions of this nerve, and by meningeal branches of the vagi. The nerve supply of the dura also includes sympathetic fibers to the blood vessels and meningeal branches of the hypoglossal nerve. By way of complex anastomoses with the trigeminal and the vagus nerves, other cranial nerves may act as vehicles for the transmission of afferent impulses. Penfield<sup>2</sup> has called attention to the presence of sympathetic nerve fibers in the walls of the blood vessels of the pia mater which arise from the sympathetic nerve plexus of the internal carotid and vertebral arteries. Foerster<sup>3</sup> considers the central roots of the trigeminal nerve to form a functional unit which can become active upon initiation from any part of the periphery and produce the symptom of headache. According to Head,<sup>4</sup> pain impulses may cause perception of pain in the thalami, without rising to the cortex.

The following are some of the theoretical factors in the initiation of headache:

1. Stretching and torsion of the dura.
2. Alterations of intraventricular pressure which result in headache following lumbar puncture and in obstruction of the ventricular system by tumors, inflammation, etc.
3. Small foramina of the veins leaving the skull.

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4. Toxic or irritative stimuli.
5. Lowered threshold for pain perception in certain persons.

During intracranial operations under local anesthesia, neurosurgeons have observed that incision of the dura causes little or no pain except near the base of the brain and over the middle meningeal artery when it is clipped and divided. The brain itself is insensitive to puncture and to incision.

A few of the organic lesions of the head which may give rise to the symptom of headache are:

1. Diseases of the brain—concussion, tumor, abscess, gumma, cyst, encephalitis, hydrocephalus, pituitary lesions, general paresis.
2. Diseases of intracranial vessels—hemorrhage, thrombosis, embolism, aneurysm, syphilitic endarteritis, arteriosclerosis.
3. Diseases of the meninges—meningitis of all types, including syphilis; and tumors.
4. Diseases of the skull—tumors, tertiary syphilis, sinusitis, pus or tumor in the orbit, diseases of dental origin.
5. Diseases of special sense organs—errors of refraction, iritis, glaucoma, conjunctivitis, melanotic sarcoma, otitis media.
6. Adenoids, nasal polypi, sinusitis.

The numerous types of headache of toxic and of "functional" origin will not be mentioned in this discussion.

In the analysis of headache as a symptom, it is of primary importance to obtain an accurate history which includes the character, location, and duration of the pain, the time of occurrence, and its relation to other factors such as reading, fatigue, and function of the gastrointestinal tract.

The severe paroxysmal attacks of major trigeminal neuralgia must be differentiated from other forms of neuralgia and headache. Recurrent headache which increases in severity and is accompanied by nausea and failure of vision, should suggest the possible presence of brain tumor.

In every case after a careful history has been obtained, rapid orientation may be established by the following procedures:

1. Complete physical and neurological examinations.
2. Examination of the blood and a Wassermann test.
3. Urinalysis.
4. Ophthalmoscopic examination.

The ophthalmoscope should be used in every case of headache to determine at once the presence or absence of papilledema. If this condition is present, investigation may then be directed toward the



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establishment of a cause for increased intracranial pressure. Lumbar puncture and examination of the spinal fluid often will give direct evidence of a pathological condition of the central nervous system, such as increased intracranial pressure, meningitis, encephalitis, or syphilis.

In cases of headache which recurs intermittently for a long period of time, severe headaches of undetermined origin, and headaches which fail to respond to treatment directed toward a supposed cause or toward symptomatic relief, a roentgenogram of the skull should be made. By this means alone, an experienced roentgenologist may be able to reveal absolute evidence of an organic intracranial lesion. In some cases it may be necessary to resort to ventriculography or to encephalography in an attempt to localize a suspected lesion of the brain.

Cooperation of the neurologist, the neurosurgeon, the internist, the ophthalmologist, and the otolaryngologist will result in the revelation of the underlying causes of most headaches. Some patients regard headache as a symptom of minor importance, and in some cases it may be true, but a clear explanation of the reasons for special examinations often procures the cooperation of the patient which leads to a solution of the cause of headache. The keynote should be careful investigation of the case with the object of determining the cause of the headache. In this way only can rational therapy be instituted.

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## HEADACHE OF ALLERGIC ORIGIN

I. M. HINNANT, M.D.

Today, one does not consider the study of the symptom headache complete without an analysis of the rôle that allergy may play. It has long been recognized by the layman that in certain individuals, certain foods would produce headaches which vary in severity from the mildest forms to the most annoying types. This general knowledge was held by the laity for many years before the entrance of food allergy into the field of diagnostic and therapeutic medicine. One readily recognizes that with the coming of the study of allergic patients, all problems are not solved, but that it does add another therapeutic aid to the armamentarium of the physician. This important field has withstood its trials and has definitely been accorded a place in medical thought.

That headache is a common symptom in patients who have allergy is an established fact, and this is due to the diversified phenomena seen in allergic patients. Three outstanding types of headache are associated with allergy:—first, those headaches which are associated with respiratory allergy; second, those associated with gastro-intestinal allergy, and third, those associated with the migraine syndromes.

In the work at the Cleveland Clinic in the past two and one-half years, we have observed a large group of patients with seasonal and perennial respiratory allergy. Those with perennial symptoms are seen twice as frequently as those with seasonal symptoms and of those with perennial nasal allergy, about 30 per cent complain of headache. This usually is of a dull frontal type, with an area of pressure in the paranasal regions, and often there is pain in and about the eyeball. These headaches are part of the symptom complex of the hay fever attack which may or may not be associated with gastric symptoms, and their severity depends to a large extent upon the degree of involvement. The frequency likewise is associated with the frequency of the attacks of hay fever. The symptoms as a rule are most severe during the winter season, which is due primarily to environmental and climatic circumstances.

In the patients with seasonal allergy—and these are chiefly those patients who are sensitive to pollens—the headache is not as frequently a symptom as it is in the perennial type, but it is more severe, and naturally, of short duration. With the swelling of the mucous membranes of the respiratory tract, and in those patients with closure of the eustachian tubes, a generalized aching and sense of fullness presents a very annoying symptom. It has been considered that the mechanism of this type of headache in the patient with respiratory allergy was due entirely to swelling of the mucous membranes and consequent pressure; however, one also must consider the low grade

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or acute toxemia that necessarily is present, and that the headache is simply one of toxic origin, as are the other symptoms of fatigue, irritability, anorexia, and insomnia.

This dull type of frontal headache which is associated with symptoms suggestive of congestive phenomena is frequently seen in the presence of hypothyroidism and hypometabolism. Allergic patients frequently are found to have low basal metabolic rates and attention to these conditions also has resulted in a higher percentage of satisfactory clinical results.

In both the seasonal and in the perennial cases of respiratory allergy, the symptoms are readily amenable to treatment. Satisfactory relief from all symptoms has been secured in 95 per cent of the patients sensitive to pollen, and in 80 per cent of those with perennial allergy.

The consideration of food allergy as a factor in the production of headache leads to a larger field. Two distinct types are recognized so far as symptoms and degree of severity are concerned. One distinctly is not of the migraine type, although it is associated with symptoms referable to the stomach or colon. This headache is usually mild, it occurs at frequent intervals, and is attended by mild gastric symptoms such as a feeling of nausea, uneasiness, halitosis, regurgitation, or mild epigastric discomfort which is suggestive of pyloric spasm. These headaches last a few hours, disappear slowly and reappear very frequently. The patient seldom is incapacitated, but is annoyed constantly by this mild symptom complex.

The mention of migraine opens a wide field for medical conjecture, and one acknowledges that no more complex problem could face the therapist. Food allergy does not explain all cases of migraine, nor does dietary control based on allergy studies relieve all symptoms. However, we acknowledge today the persistent and thorough work of Rowe, Vaughan, Rackemann, and other workers in the field of allergy, and welcome the promising results these men have obtained.

In a diagnostic clinic, patients with migraine very frequently are encountered. This is due primarily to the failure of these patients to obtain satisfactory relief by use of the usual measures prescribed. They present themselves in the hope that an unknown etiologic factor may be discovered. In our survey of patients with migraine, an investigation of the factor of allergy always is included. The effort expended in this study usually is rewarded proportionately.

In a consideration of migraine, the question immediately arises in regard to which group of patients food allergy may be an important factor. A careful history which reveals any personal or family history of allergic manifestations is helpful. In this group of patients, one usually sees the most encouraging results after the allergy factor has

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been investigated and controlled. Vaughan<sup>1</sup> reports a positive family history in 70 per cent of his patients who have migraine due to allergy. We, likewise, have been able to elicit a positive family history in the majority of our cases. Personal allergic manifestations, such as eczema, hay fever, asthma, and urticaria, anticipate the more definite factor of food allergy as an etiologic agent.

Granting the possibility of an allergic factor in the etiology of migraine, what diagnostic methods may be used to identify the causative agents? The impression of some physicians that allergy studies are of little value in identifying causative foods is erroneous. We find that skin tests with standardized extracts give about 60 per cent accurate results in cases of food allergy. If repetition of the tests does not increase the amount of information, then further study of dietary influences through elimination diets and food diary trial should be made. Probably the laboratory procedure of greatest value in cases of food allergy is the leucopenic index of Vaughan<sup>2</sup> which is based on the principle of hemoclastic crisis as pointed out by Widal, Abrami and Iancovescu<sup>3</sup> in 1920. The ingestion of foods in normal patients produces a mild leucocytosis. In patients with food allergy, the ingestion of foods to which the patient is sensitive produces a marked leucopenia. Through this simple laboratory procedure, offending foods have been discovered when skin tests, elimination diets, and the food diary have failed. In the experience of Vaughan and other workers, this test has been from 90 to 100 per cent accurate.

At the Cleveland Clinic, we have seen a number of cases of so-called bilious attacks in children. These attacks consist primarily of gastrointestinal symptoms, but headaches always are present, which vary in the degree of their severity. Other evidences of allergy such as rhinitis, conjunctivitis, or urticaria may or may not be present at the time of attacks. These patients have been carefully examined, and it has been found that their symptoms were due essentially to allergy. Complete relief usually has been obtained from dietary management which was based on the results of the allergy studies and follow-up reports from these patients have been very encouraging.

What foods are factors and what dietary problems arise in the solution of these manifestations of headaches? Both skin tests and clinical trial have shown that the common foods—wheat, milk, eggs, chocolate, coffee, potatoes, beans, peas, and bananas—are causes in the order named. Dietary management usually demands special care, but no disturbance of the patient's nutrition need be encountered if adequate attention is given to regulation of the diet. This has been found to be true particularly in the group of children with food allergy in whom the state of general nutrition has improved and other general

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symptoms have disappeared after dietary management has been instituted which was based on the studies for allergy.

No comment on migraine or the syndromes which simulate migraine is complete without some discussion of the agents which give symptomatic relief regardless of the etiological factors, the severity, or the duration of the pain. In our experience, and in the experience of other workers, the oral, hypodermical or intravenous administration of ergotamine tartrate has given remarkable relief to these patients. The oral administration of 2 mg. of ergotamine tartrate at the onset of symptoms will give satisfactory relief in from 30 to 90 minutes, while the hypodermic or intravenous administration of 0.5 mg. gives relief in from 15 to 30 minutes. As a rule, no ill effects are encountered, and symptoms of nausea and occasional vomiting are transient. Patients can easily be taught the use of the syringe and needle so that no delay is necessary in receiving the drug at the opportune time. No other drug has been found which will give immediate relief from this headache.

In this presentation, the discussion of allergy as a factor in the production of headache has been limited to general principles. Further observations and more detailed data will be reported later. However, one important fact which must be acknowledged is that allergy may be wholly or partly responsible for the headache of a certain group of patients. Our results have been very encouraging, and we believe that more thorough and persistent effort in this field will give a larger percentage of patients with satisfactory clinical relief from their symptoms. It is necessary to recognize that every phase of the patient's problem must be thoroughly studied, and untiring effort be given in the study of allergy.

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## HEADACHE OF SYPHILITIC ORIGIN

E. W. NETHERTON, M.D.

Although there is nothing pathognomonic about the headache which results from syphilis, this disease should be considered in the differential diagnosis of all cases in which persistent or recurring headache is a chief complaint. Since the *Spirocheta pallida* has a predilection for blood vessels and since many of the late manifestations of the disease occur in the central nervous system, it is not surprising that syphilis is an important cause of headache which may precede other symptoms and neurological signs by a long time.

No one would contend that headache which occurs in a syphilitic patient is necessarily related to his infection; however, the physician's responsibility to the patient makes it necessary that a thorough investigation for evidence of central nervous system syphilis be made. A careful neurologic examination and a spinal puncture are indicated. Equally important is a careful ophthalmological examination which includes examination of the visual fields for evidence of optic neuritis.

Most patients with early secondary syphilis complain of headache. It may be very slight, dull or paroxysmal, or in some instances, the pain may be severe and associated with slight stiffness of the neck. The associated cutaneous and mucous membrane lesions and positive serologic findings will simplify the diagnosis.

In late syphilis, headache results either from the involvement of the vessels of the brain or from an inflammatory reaction of the meninges, particularly the dura mater. Such cases are classified as vascular or meningovascular neurosyphilis, and the latter is the most common type. Headache may occur in the presence of parenchymatous neurosyphilis, such as paresis, but it is seldom a major complaint. In practically all cases of late neurosyphilis, signs and symptoms referable to syphilitic meningitis eventually appear. This is true especially in those cases which receive little or no treatment. The severity of these manifestations depends upon the location and the intensity of the inflammatory reaction.

The headache which accompanies vascular neurosyphilis usually is diffuse, dull and stupefying in character; however, occasionally it is localized. The pain is seldom constant, and it may disappear for weeks at a time and then return without any apparent cause. It may be the only symptom in some cases, and in others, attacks of dizziness, insomnia and personality changes frequently are associated symptoms.

The headache produced by syphilitic basal meningitis is located deep back of the eyes, and often it is very severe. The patient complains of pain when pressure or percussion is applied over the brow. Optic



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neuritis usually is present, and cranial palsies frequently occur. Involvement of the convexity of the brain produces a diffuse headache associated with localized areas of tenderness on the scalp. The patient complains of a pressing sensation on the vertex of the scalp.

Gumma of the brain is a rare condition in which the headache is the same as that which results from intracranial pressure produced by neoplasms. Examination of the spinal fluid in gumma of the brain and in vascular types of neurosyphilis frequently gives normal findings while in the meningovascular type, one usually finds varying degrees of pleocytosis, increased globulin content, a positive gold chloride reaction, and a positive Wassermann reaction. There are, however, cases with unmistakable signs and symptoms of syphilitic basal meningitis in which the spinal fluid findings are normal. One of the most constant findings is an increase in the total protein content of the fluid. Likewise, too much dependence should not be placed on negative blood Wassermann reactions because it is not uncommon to find normal serum in late syphilis. As in all laboratory procedures, the physician must correlate the serologic findings with the symptomatology and the clinical findings in each case.

Neurorecurrence is an important and often unrecognized type of neurosyphilis in which headache is one of the common symptoms. It is very important that this condition be recognized early, because prompt institution of intensive arsphenamine therapy will influence the prognosis in such a case. Neurorecurrence is a relapse of an inadequately treated infection which usually occurs early in the course of the disease, and in cases which have received only a few injections of some arsenical preparation; however, it may develop during the time when the patient is receiving fairly intensive treatment. The onset of symptoms may be sudden, but frequently it is gradual. The patient may complain of intense headache, associated with nausea and vomiting, and cranial nerve palsies may develop. Examination of the spinal fluid shows a marked pleocytosis. In all cases of early syphilis in which headache develops during or after inadequate treatment, a spinal puncture should be performed. If evidence of meningitis is present, the treatment should be prolonged and intensified with arsphenamine, supported by bismuth and mercury. The response to treatment should be checked by repeated examinations of the spinal fluid, and if the fluid is abnormal after continuous and intensive therapy for 18 months or two years, malarial therapy should be administered.

Headache is a common symptom of hemorrhagic encephalitis—a complication which rarely follows arsphenamine therapy but which must be differentiated from neurorecurrence. In hemorrhagic encephalitis, the headache is severe, the patient is very nervous, excitable and hyperkinetic and these symptoms usually appear early in the

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course of arsphenamine therapy. The cell count of the spinal fluid is normal or only slightly increased in the presence of encephalitis, while in neurorecurrence there may be a marked pleocytosis.

Syphilis is a common disease and neurosyphilis develops eventually in a large percentage of the infected individuals. Because of this, the possibility of syphilis as an etiological factor in the production of headache should be kept in mind.





## THE PRESENT STATUS OF THE DIAGNOSIS OF RENAL TUMORS\*

B. H. NICHOLS, M.D.

When one considers the high rate of mortality associated with renal tumors and the advanced stage of their development before a diagnosis is made, and that metastatic lesions are often the first sign of the disease, one is at once impressed with the importance of any new diagnostic developments in this field. A correlation of such information has been my aim in this presentation.

First of all, it is assumed that at the present time a roentgenologist undertaking the examination of a patient suspected of having a renal tumor is a capable clinician who is familiar with the history, symptoms and course of such lesions, together with the morphology, pathology and possibilities of behavior at any stage of their course and also with the pathologic conditions of the kidney and surrounding areas which must be taken into consideration in making a differential diagnosis. Many times by a process of elimination of possible causes of the symptoms a diagnosis of renal tumor may be made when a direct attempt at making such a diagnosis would fail.

The recent developments in the diagnosis of kidney tumors reported in the literature have been rather limited to case reports and to the emphasis of complications encountered accompanying such lesions. I have attempted to abstract from these reports such information as may be of aid to the roentgenologist in reporting his findings.

In summing up a paper on "Tumors of the Renal Pelvis," MacKenzie and Ratner<sup>13</sup> conclude:

"The disease is very often wrongly diagnosed and the diagnosis must be made from the history, symptoms, urinary findings, cystoscopic and pyelographic findings."

In the past many roentgenologists have been content to confine their diagnostic contribution solely to the field of roentgenology, anticipating that all other clinical help would come from the urologist. This has been a quite satisfactory arrangement since the urologist was usually the one who referred the patient and the only one capable of cystoscopic examination, catheterization of the ureters, and injection of the kidney pelvis before a pyelographic examination could be made. But with the newer development of excretion urography the roentgenologist has added responsibilities, for many patients are referred direct to him.

Many times all the information obtainable after such an examination will not be sufficient to solve the problem, but in such cases the fact

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that the patient has a definite kidney lesion can usually be determined and he can then be referred to a urologist for further examination.

The status of excretion urography in the diagnosis of renal neoplasm should be carefully considered. The situation of most palpable masses in the region of the kidney may easily be determined to be outside the kidney by an excretory urogram which usually shows clearly that the kidney pelvis and kidney are extrinsic to the palpable mass. The diagnosis may become difficult in the case of a tumor arising from the capsule or of a perirenal tumor attached to the kidney, and if there is no deformity of the pelvis neither excretory nor retrograde pyelography will be of much diagnostic value except in a negative way. Excretory urography often shows characteristic distortion of the pelvis and calyces in tumors of the kidney proper, together with a fair estimate of function in such a kidney.

Recently in a paper on renal tumors Wade<sup>24</sup> has stated:

"My theme in brief may be stated to be based essentially on the relative roles of infusion and excretion urography. (Infusion urography indicates form.) (Excretion urography indicates function.) The former is the primary diagnostic aid for the recognition of the presence of a tumor of the kidney. The latter, by indicating the state of the adjacent renal parenchyma, is a valuable aid in identifying the type of growth that is present.

"This knowledge not only permits of a more accurate preoperative prognosis but also thereby gives warning of some of the complications that may be met. Of these the most important are: the daughter tumor concealed in the ureter in a villous papilloma of the renal pelvis; the accessory venous circulation in the perinephric fascia due to a neoplastic thrombus in the renal vein in cases of hypernephroma or papillary carcinoma; the involvement of the renal pedicle and the adjacent lymph glands in cases of alveolar carcinoma.

"In other types of tumor, such as the epidermoid carcinoma and the embryonal carcinoma, and the rare tumors, information of similar value is also obtained. It amounts to this: 'The degree of malignancy of a tumor of the kidney is in inverse proportion to the functional activity of the organ as a whole.'"

In the discussion of this paper Dr. Braasch stated:

"My experience coincides to a very large degree with that of Mr. Wade as to the value of intravenous or excretory urography in the differential diagnosis of renal tumor. (I will say, however, that if we relied upon the intravenous urography entirely, we would frequently find ourselves in difficulty. It may be quite misleading.)

"I agree with Mr. Wade that unless a man is skilled in the diagnosis and interpretation of pyelography, he should not attempt to employ



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intravenous urography. Unless the details of the pelvic deformity are clearly visualized, interpretation may be frequently misleading. I have observed a number of intravenous urograms in which we might infer that we are dealing with a normal pelvis, where neoplasm was found to be present when the retrograde method of pyelography was employed.

( "Secondary infection or reflex irritation may affect the degree of visualization with intravenous urography, so that great care must be employed in its interpretation. ) (The two methods of intravenous and retrograde urography are often very valuable when combined. ) (Very often intravenous urography is distinctly better than the retrograde method, when there is obstruction at the ureteropelvic juncture or retention of urine in the pelvis. )

Excretion urography has become one of the most important advances in roentgenology, not even surpassed by cholecystography. An excretory urogram may be safely done and all the necessary evidence found for the diagnosis of a renal neoplasm in most cases. Further examination by a retrograde pyelogram if catheterization of the ureter is possible may give much added information and should always be resorted to in all cases where there is any doubt about the diagnosis.

Careful attention to the technique of the latter examination is necessary. Wilson<sup>26</sup> in an excellent paper on the diagnosis of renal tumors warns against a mistaken diagnosis in an incompletely filled pelvis. This may come about either by failing to insert the catheter high enough, with a consequent reflux into the bladder, or by attempting to fill a kidney pelvis with an opaque medium, when it is already full of retained urine or blood clots. This pitfall may be obviated by draining the pelvis before a pyelogram is attempted and by repetition of the examination when there has been any question of the cause of a filling defect in the kidney pelvis.

Within the last decade another method of roentgenographic diagnosis of the kidney has received considerable mention in the literature, namely, pneumopyelography. All roentgenologists should be familiar with the advantages and disadvantages of this method.

Thompson<sup>23</sup> in 1922 wrote:

" . . . The injection of gas into the renal pelvis for roentgenologic purposes has not been popularized to the extent that it deserves, . . . the technique of which is simple and the advantages numerous. . . . The injection of oxygen into the ureter or renal pelvis causes no shadow at all but creates a space which shows up black on the x-ray plate, and brings into relief not only the pelvis and calices, but also the kidney tissue, as it does not obscure the shadows caused by the tissues either in front or behind. For instance, the shadow of a stone in the ureter, pelvis or calix will not be obscured by the oxygen and the size, shape

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and position of the stone can be easily determined. . . . So far in our group of cases only oxygen has been used in pneumopyelography which meets fully the requirements of a contrasting media, in that it is not toxic and not irritating and may even be beneficial in some cases. As oxygen is more permeable than any of the opaque solutions, it will pass obstructions or constrictions more readily than the solutions."

The author then describes his technique of examination, and illustrates one case of stone with hydronephrosis, the stone not having been demonstrated by pyelogram with an opaque medium, and concludes:

"1. Pneumopyelography is a simple, though uncommon, procedure and deserves a greater popularity.

"2. This procedure is attended by apparently no reaction and causes the patient less discomfort than the injection of an opaque solution.

"3. In certain cases it is a greater aid in roentgenographic diagnosis, than the opaque solutions."

Neuwirt<sup>18</sup> has stated that he regards this procedure as the method of choice in the diagnosis of nephrolithiasis.

"It will disclose the smallest stones more often and better than pyelography alone. Even simple incrustations stand out very clearly. Furthermore, one examination suffices to obtain all the information needed. The author has found it to be the only method which made possible a diagnosis of a tumor of the kidney pelvis or of the ureter. In cases of tumor of the kidney parenchyma, pyelography is the method of choice. Bleeding from the pelvis of the kidney is not a contraindication to the method."

Chauvin, Empéaire, and Esmenard<sup>2</sup> advise the injection of air under a constant manometric water pressure of 80 cm. They claim that it is painless and safe as it allows of a wide margin of safety from any possibility of air embolism. They say:

"The especial value of the method lies in the exact localization of calculi, and in the demonstration of those of little density, when an opaque medium merely conceals; further, papillomata of the renal pelvis are shown, and large hydronephroses may be filled with impunity."

Tasker in an abstract of an article by Bedrna and Simon<sup>1</sup> states:

"The author discusses the difficulty in the diagnosis of tumors of the renal pelvis from other causes of unilateral renal hemorrhage. Ordinary pyelography may show large tumors as a filling defect, but small papillomata are likely to be hidden by the shadow of the opaque fluid. When small tumors of the renal pelvis are suspected he advises pneumopyelography. Ordinary atmospheric air is injected by a 20 c.c.

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syringe into the renal pelvis through a small ureteric catheter, the injection being made slowly. In 345 cases no complications followed.

"A difficulty in diagnosis by this method is blood-clot in the pelvis, as the shadow from the x-ray may resemble a papilloma. For this reason repetition of the pneumopyelography is advised after some days. If the shadow has not altered, a tumor is probable, but if due to blood-clot then the shadow will have altered or disappeared. Details of two cases are given in which this method enabled a correct diagnosis to be made."

Jeck<sup>8</sup> has reported a case of air embolism which proved fatal. This was the only death in his six years' experience with inflation of the bladder in cases of suprapubic cystotomy.

Mathé<sup>16</sup> reported a case of fatal air embolism from inflation of the bladder. The patient was a man, aged fifty-six, with hypertrophy of the prostate, chronic retention, an ulcerated bladder neck and a papillomatous growth on the base of the bladder about 4 cm. in diameter. A suprapubic approach was decided upon and the bladder was inflated with 300 c.c. of air. After a few seconds, and while the first sutures were being taken in the fundus, a hissing sound in the bladder was heard. The patient became cyanotic, the eyes fixed, the pupils dilated, and the pulse and respiration suddenly ceased. All attempts at resuscitation were futile. At necropsy, air was found in the iliac and mesenteric vessels, the vena cava and the renal veins. The lungs, liver and the right chambers of the heart contained coarse, frothy air. Following this fatal accident, Mathé made an extensive investigation of the problem during which time he sent out 2,050 questionnaires to surgeons doing genitourinary surgery in this country and abroad and received 791 replies. In 25,890 inflations with air, there were 34 cases of air emboli. He states that air under pressure in the normal bladder and ureter causes no harm, but says,

"The formation of emboli takes place by the entrance of air into the venous circulation either through an ulceration of the mucosa caused by some pre-existing pathologic lesion such as an ulcer, a tumor, a deeply congested area due to cystitis, etc., or through a laceration of the mucosa caused by over-distention of the bladder. . . . Once the veins of the bladder wall are ruptured, a minimum amount of pressure can cause penetration of air into the vesical veins and thence into the vena cava and right heart."

Lewis<sup>21</sup> theory is that the air enters into the circulation by way of the pelvis of the kidney after having regurgitated through the ureter. Santini's<sup>20</sup> experiments did not support this theory. He injected air under considerable pressure into the healthy bladders of dogs and found that the healthy bladder invariably ruptured before air would enter the kid-

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ney pelvis through the ureter. When he injected air into the abdominal portion of the ureter, he found that air could be introduced into the circulation by way of the renal parenchyma. Piddighe,<sup>19</sup> experimenting with 11 dogs, could not support the latter part of Santini's work. He injected air into the lumen of the ureter under considerable pressure for from fifteen to thirty minutes. This caused considerable increase in the volume of the kidney but death from air emboli could not be produced. Subsequent autopsies showed considerable dilatation of the pelvis and tubules, but in no case was he able to demonstrate air in the circulation. However, when the veins of the bladder wall were traumatized, inflation of the bladder with air under low pressure caused death in a few minutes. In these dogs, at necropsy, the usual pathologic picture of air emboli was found.

Mathé concludes:

"Rupture of the vesical mucosa by over-distension, or the presence of a pre-existing pathologic lesion such as marked inflammation, ulcer formation, or a new growth weaken the bladder wall thus favoring the entrance of air into the venous circulation."

This is a very excellent and comprehensive study of air emboli and includes a long bibliography. It includes a summary of 23 collected cases of air emboli with 18 deaths.

We are doing an increasing number of pneumopyelograms, particularly in cases in which pelvic papillomatous tumors are suspected. These have been performed with no discomfort to the patient. Our feeling is that if the catheter is not tightly gripped in the ureter, as occurs in case of a stricture or ureteral stone, there is little danger of creating a pressure in the kidney that would be at all hazardous, as the air will reflux into the bladder when the pelvis is filled. Roentgenograms are made while the air is being injected. This method of examination has some very distinct advantages in the diagnosis of pelvic tumors or kidney stones.

Pyeloscopy is another technique for the examination of the kidney which has been used by some workers for many years, but has not received widespread attention in the field of renal diagnosis. An excellent article by Herbst<sup>6</sup> outlines its particular sphere of usefulness and a statement which he quotes from Jona and Flecker would seem to have an important bearing on the diagnosis of tumors. They found that atropine definitely decreased the activity and produced relaxation of the pelvis to the point of painful distention which was in turn relieved by the administration of eserine. It seems reasonable that in cases in which function is not a consideration, or after the determination of function by excretory urography, repetition after the administration of atropine might better outline the deformity of the kidney caused by a renal tumor.

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In another article by Manges, who introduced the pyeloscopic method in 1912, and who has had a long experience with it, its advantages in the diagnosis of renal tumors are outlined as follows:

"The fourth advantage comes in being able to palpate the movable kidney, and at the same time, see what the effect of palpation or manipulation is in the matter of rotating the kidney or determining the extent of its mobility. . . One also palpates tumor masses that are present in the abdomen and in this manner can determine very definitely whether the mass is attached to or a part of the kidney, even when there is not deformity of the pelvis and calices due to the involvement of the tumor."

The ambition of most clinicians is an attempt to determine the type of tumor with which they are dealing. This, of course, would be ideal but a glance at the great mass of controversial literature on the classification of renal neoplasms makes it an impossibility for all practical purposes at the present time. If the pathologists cannot agree on the type of tumor after examination of the sections, how much more difficult is it for the clinician and roentgenologist to determine the specific type of lesion? If one can determine the presence or absence of a kidney tumor along with a fairly accurate estimate of whether it is malignant or benign, an admirable service has been rendered to the patient and to the surgeon.

A recent article by Gottesman, Perla and Elson<sup>4</sup> illustrates the difficulties encountered in the diagnosis of specific tumors. They reported the pathologic findings in 44 cases of hypernephroma. Sixteen of these were found by chance at autopsy. Some of the specimens showed all gradations from benign structure to malignant hypernephroma in the same tumor. Cortical adenoma, typical hypernephroma, papillary and adenomatous malignant areas, and also carcinomatous and sarcomatous-like infiltrations were observed.

There apparently is no classification of renal tumors to which all are agreed. Graham<sup>5</sup> disposes of this subject in a practical manner:

"Comparative statistics concerning the incidence of the various types of renal neoplasms is increasingly difficult to obtain from the numerous clinics where comparatively large numbers of these cases are treated. This is due chiefly to differences in the interpretation of the two most frequently encountered types of neoplasms, namely, hypernephroma and carcinoma. It is not surprising, therefore, that in one clinic about 80 per cent of all malignant renal neoplasms may be classified as hypernephromata, and in another clinic less than 30 per cent are so classified. It is highly improbable that the Grawitzian tumor is less prevalent today than it was twenty-five years ago.



*"Hypernephroma.*—The type of lesion described by Grawitz is the most frequently encountered, and, therefore, is the most important neoplasm of the kidney. That it originates in adrenal cortical tissue, which is included in the kidney during its developmental period, has been disputed recently. Whatever may be the final judgment in the matter, segregation of this group of tumors seems amply justified by embryological, gross, microscopical, chemical and clinical considerations.

*"Carcinoma.*—Second in order of frequency and importance among renal neoplasms are the carcinomata, which may be considered under two groups: (a) those arising from tubular or glandular epithelium, and (b) those arising from the pelvic mucosa.

*"(a)* Probably the most important source of carcinomata in the substance of the kidney in adults is the adenoma, occurring with comparative frequency.

*"When the adenoma becomes malignant (carcinoma),* fairly well circumscribed or diffusely infiltrating neoplasms of considerable size may result. Clinical manifestations (pain, hematuria, palpable tumor), anatomical alterations, and abnormalities noted in roentgenograms and pyelograms naturally depend upon the location, size, and rate of growth of the tumor, and whether or not the pelvis is secondarily involved.

*"(b)* Carcinomata arising in the renal pelvis are of two types—papillomatous and epidermoid.

*"Sarcoma.*—True sarcoma in the sense of a malignant tumor arising from the supporting tissue (capsule, stroma, or adventitia of blood or lymph vessels) is rarely observed in the kidney as a primary tumor. A rather hurried search of the records of the Cleveland Clinic for the past eight years has failed to disclose a single case. It is more than probable that a large percentage of cases appearing in the literature under the heading of sarcoma would be more appropriately classified as cases of embryonal carcinoma or of mixed tumor of one type or another.

*"Mixed tumors.*—Mixed tumors constitute the third group of renal neoplasms in order of frequency and importance. They are not a homogeneous group and do not conform to a type. In this group are included tumors which are probably variable in derivation, and certainly variable in composition. The one feature that characterizes them as a group is the fact that they comprise the majority of renal neoplasms which occur in childhood.

*"Extra-renal tumors.*—*Lipomata* may develop in the peripelvic fat of normal kidneys and result in displacement of the organ and deformity of the pelvis. They may develop in the fat which is deposited in kidneys that are atrophic as a result of interference with the circulation or as a result of chronic infection, with or without calculus, or they may



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develop in the perirenal fatty capsule and by their size misplace an otherwise normal kidney.

"*Fibromata, fibrolipomata, or fibromyxomata* may develop in the perirenal tissue. The myxomata may either be encapsulated or diffuse and may become sarcomatous. These tumors may displace, but usually do not invade, the kidney.

"*Retroperitoneal neoplasms* such as lymphoblastoma, common sarcoma, endothelioma, and tumors of the adrenal may simulate renal neoplasms.

"*Subhepatic, intrahepatic, subdiaphragmatic, or psoas abscesses and omental and mesenteric cysts* may simulate cystic tumors of the kidney."

I use Ewing's<sup>3</sup> classification of tumors of the renal pelvis which meets the need of the roentgenologist for it is convenient and workable.

*Papilloma.*—These are usually multiple and large papillomas may be surrounded by smaller ones. Papillomas may be associated with calculi. Papillomas are very vascular tumors and bleed easily. They are usually benign, but tend to become malignant and give rise to transplants along the ureter and in the bladder. They constitute about 50 per cent of the pelvic tumors of the kidney.

*Papillary Epitheliomas.* These are wartlike growths, which in the early stage involve the submucosa, but later extend into the renal parenchyma. Late stages of the growth may be accompanied by cortical cysts. These are very vascular tumors and hemorrhage is frequent. Papillary epithelioma makes up about 20 to 30 per cent of kidney pelvic tumors.

*Alveolar Carcinoma.* These are probably late papillomatous growths which have lost their papillomatous formation and form scirrhous type of growths. These are large tumors, have a high degree of malignancy, and metastasize widely.

*Squamous Cell Carcinoma.* This type of tumor forms a very small group. They are characterized by rapid growth, extensive metastases, infiltration of the surrounding tissues and kidney parenchyma, and rapid fatal termination.

Since the pathologists themselves have such difficulty in making an exact diagnosis in cases of kidney tumor, the roentgenologist cannot hope to report a specific type of tumor in a given case with any high degree of accuracy. And there are always certain cases in which some doubt remains even after the most careful clinical, roentgenologic and pathologic study, and it is literally impossible to make any accurate predictions regarding the final outcome.

The following cases will serve to emphasize some of the difficulties of diagnosis, and the necessity of giving a guarded prognosis even

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though the histopathology of a given tumor is indicative of a relatively hopeful outcome:

CASE I. A woman, aged fifty-four, was referred to me for examination by Dr. W. E. Lower, on July 29, 1929. Her chief complaint was "weakness and fullness in the stomach." In January, 1929, she had influenza, and about this time had developed a frequency and burning on urination. She had become quite constipated, and had lost 40 pounds.

When she presented herself for treatment, there was a large mass in the left hypochondrium which extended to the crest of the ilium and across the midline into the right side of the abdomen. The clinical impression was that this mass was caused either by an enlarged spleen or left kidney. The renal function as determined by the phenolphthalein test was 70 per cent. The cystoscopic examination disclosed no abnormality, but urine specimens from both kidneys contained a moderate number of pus cells. The roentgenogram of the kidneys, ureters and bladder showed a large mass in the left kidney region which appeared to be extrarenal. The pyelogram showed hydronephrosis, and displacement of the ureter and the kidney beyond the right of the midline by a large mass. The pyelographic diagnosis was a probable tumor of the left kidney.

Operation was performed by Dr. Lower on August 14, 1929. A large mass measuring about 11 x 15 cm. was attached to the kidney. Visible renal tissue appeared grossly normal. The tumor surrounded and included the left kidney. The kidney was easily removed from the mass, leaving a well-formed depression. Toward the upper pole of the kidney, lying outside of the well-encapsulated main portion of the tumor, was a mass of fat tissue which was not encapsulated and had a consistency that suggested the possibility of myxomatous change. The blood supply of the whole myxomatous mass was not very abundant. Fetal lobulation persisted. One microscopic section was made up of myxomatous tissue. There was a fibrous capsule and external to this was a small amount of fat. Histologically it did not appear to be very malignant. Another section was made up of fibromyxomatous tissue, the fibrous predominating; a small amount of fat was scattered through the sections which histologically appeared benign. The diagnosis was perirenal myxoma.

This patient returned again to the Clinic, on September 11, 1933, with a recurrent, extensive, inoperable mass which practically filled the entire abdomen and probably involved the intestines. The chest roentgenogram showed no evidence of metastases.

This represents one of a group of tumors which are potentially malignant in that they recur locally but do not give rise to distant metastases.

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**CASE II.** This patient was a man aged fifty-four, first observed in November, 1923, who complained that he had had a nervous breakdown six months previously, and that he felt below par on arising in the morning. During the day he felt well. He also complained of vague gastrointestinal disturbances which seemed to be associated with his nervousness. There were no genitourinary symptoms except that he had had one sharp attack of back pain sometime previously which had gradually disappeared and had not recurred. The physical and laboratory examinations gave no clue to his complaints and his hemoglobin was 90 per cent. He was reassured and advised to get additional rest in the belief that the condition was one of neurotic origin.

He returned again in August, 1927, stating that his endurance was poor and that he had had another attack of back pain during the previous year which had gradually improved and was then absent. Since this last attack of pain his appetite had been poor. He had nocturia, three times each night.

Physical examination showed nothing of significance except for a few pulpless teeth. The roentgenograms of the kidneys, ureter and bladder and of the lumbosacral region showed no abnormality. Cystoscopic examination revealed a mild trigonitis and slight prostatic hypertrophy. Since there was no clinical indication for a pyelogram, this examination was not done. Because of the vague symptoms of pain, gastric disturbances, listlessness, irritability, and his changed mental outlook, it was thought that the problem was chiefly a neurologic one.

He sought treatment again in November, 1927. At that time he had ascites and the liver was enlarged. The kidneys were not palpable and there had been no urinary symptoms except the frequency and nocturia. Exploration was resorted to and an inoperable tumor of the kidney was found. The operative diagnosis was hypernephroma of the right kidney.

This is a representative case in which the clinical history, vague symptoms and negative physical examinations certainly were not suggestive of a malignant condition, especially of the kidney. This patient developed metastases and ascites before such a lesion was suspected. Renal malignancies with such a history will probably be overlooked, unless a pyelographic examination is adopted routinely, which, most will agree, is impracticable. It also illustrates that a normal roentgen picture of the kidneys, ureters and bladder does not eliminate the possibility of a renal tumor.

**CASE III.** The patient, a physician, aged sixty-eight, had an unexplained fever which was intermittent and recurrent, sometimes rising as high as 101.5° F. He had examined his urine and had found some pus and albumin. He had some burning on urination and some diffi-

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culty in starting his stream. He did not feel unwell. He attributed the fever to infected tonsils. Physical examination revealed a right upper abdominal mass which extended to the level of the umbilicus, and chronic prostatitis. The urine examination showed no significant abnormality except an occasional red blood cell in one of numerous specimens. The Wassermann and Kahn tests were positive. Syphilis had been contracted years previously during an operation on a luetic patient. The pyrexia, the abdominal mass, which was interpreted from palpation as being the liver, and the positive reaction of serologic tests led to the diagnosis of luetic hepatitis. He was given antiluetic treatment. Six months later an excretion urogram was made for renal function incident to a prostatic punch operation, and a large deformity of the right kidney was noted; this was interpreted as being due either to an anomalous kidney or to a tumor. A pyelogram was made and this showed, with greater detail, a very large deformity of the right kidney which was interpreted as a hypernephroma.

At operation an inoperable malignancy of the kidney was found which had invaded the perirenal tissues. The operative diagnosis was hypernephroma. The patient died five months later.

This case serves to illustrate the caution which one must exercise in forming any conclusions, from palpation alone, as to the origin and nature of abdominal masses. Only one of the so-called cardinal symptoms of renal malignancy was present, and its association with an infectious process which might produce enlargement of the liver, resulted in misinterpretation of the signs and symptoms.

In connection with these cases which have presented especially puzzling diagnostic problems, I am presenting the data which have accumulated in the study of a series of cases of renal tumor seen at the Cleveland Clinic.

In 100 proved cases of kidney tumor there were 55 hypernephromas, 20 carcinomas, 3 squamous cell carcinomas of the renal pelvis, 16 kidney tumors in children, 3 cases of fibromyxosarcoma, 2 of perirenal myxoma, and 1 sarcoma. The symptoms in their order of frequency were pain, a palpable mass and hematuria. All of these symptoms were present in 25 per cent of the cases. Of the patients with hypernephroma, 55 per cent had hematuria, 28.3 per cent of these without pain.

The clinical impression included kidney tumor in 80 per cent. In 20 per cent involvement of the genitourinary tract was not suggested by the symptoms. The plain stereoscopic roentgenogram revealed a diseased kidney and raised the question of tumor in 75 per cent of the cases of hypernephroma, in 30 per cent of cases of carcinoma and in 50 per cent of the childhood tumors. The cystoscopic examination

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revealed little information in cases of hypernephroma except when blood was seen to come from the ureter. In the cases of carcinoma of the kidneys, 15.4 per cent showed transplants to the bladder. Pyelography yielded a correct diagnosis of tumor in 64 per cent of the total series and in 83 per cent of all cases in which a carcinoma was present. Excretion urography was used in only a small group of cases of kidney tumor but revealed the lesion in all instances in which it was employed.

Some recent cases culled from the literature and some additional reports from our own series serve to illustrate further some of the more rarely encountered complications and features of roentgenographic diagnosis of kidney neoplasms.

Meredith<sup>17</sup> has reported a case of kidney tumor complicated with a tuberculous infection. This patient had a papilloma of the kidney with transplants to the ureter and bladder accompanied by a tuberculous infection in the same kidney. Cystoscopic examination showed a papilloma of the bladder, and this, with the finding of acid-fast bacilli in the urine from this kidney, aided materially in making the correct diagnosis.

Kretschmer<sup>10</sup> reported a fibroma of the kidney in a man, aged thirty-eight. His chief complaint was painless and symptomless hematuria. Six years before, he had passed gross blood in the urine, followed one week later by severe pain over both kidneys and two months later he had passed a stone. The kidneys were not palpable. The physical and laboratory findings were normal, and the roentgenographic and cystoscopic examinations showed no abnormality. The right pyelogram showed a filling defect compatible with tumor. A diagnosis of a tumor of the right kidney was made and nephrectomy was performed. The kidney specimen was of about normal size. The pelvis was distended by a compact form, a grayish-white tumor 43 by 41 by 35 mm., which was attached loosely close to the large renal vessels at the root of the kidney, and all around the tumor there was peripelvic fat. There was very little compression of the renal substance by the tumor. Histologic examination showed the growth to be a fibroblastoma.

Kretschmer states that small fibromata under the capsule, in the cortex, or in the medulla at the bases of the pyramids are not infrequently found at autopsy but that they seldom cause signs or symptoms during life. "Large renal fibromata are also extremely rare and on account of their rarity they may be considered curiosities both from a clinical and pathological standpoint." He states that there have been only 11 cases of pure renal fibromata. Several theories are advanced to explain the etiology of these tumors. Ewing believes these fibromata have their origin in disturbances of development but quotes Genewein who thinks that they are not true neoplasms but are tumor-



like nodules arising from superfluous tissue. They may occur in any part of the kidney. Symptoms consist of a palpable mass, pain and hematuria. They vary considerably in size, even to filling the abdomen. The prognosis in such cases is good.

Mackey,<sup>14</sup> in 1930, reported a case of hemangioma and considered the whole problem by means of a thorough review of the literature. He stated:

"Haemangioma of the kidney is of relatively rare occurrence, and authors of wide experience frequently report only a single new case. Infrequent though it may be, it is a condition of surgical importance, for it appears that a large proportion of cases ultimately demand operation more or less urgently. In the cases published, an accurate pre-operative diagnosis has seldom been made."

MacKenzie and Hawthorne<sup>12</sup> reported 2 cases of renal hemangioma in 1931. The first patient was a man, aged thirty-five, whose complaints were hematuria of ten days' duration, slight attack of pain in the left lower quadrant of the abdomen, and general weakness for two weeks preceding admission. There were no areas of abdominal tenderness and no masses were palpable. Both kidney areas seemed normal by palpation, and the cystoscopic findings were essentially normal. The urine contained red blood cells and a few pus cells. A pyelogram of the left kidney showed a dilated renal pelvis with distorted, irregularly placed and shaped calyces at the level of the second and third lumbar vertebrae. A left nephrectomy was performed. There was a moderate amount of perirenal infiltration and the cut surface of the kidney showed hemorrhagic areas just beneath the mucous membrane of the upper calyx. The kidney showed fetal lobulation; the cut section showed a dark hemorrhagic area at the upper pole, which was made up of larger and smaller blood channels, lined with endothelial cells and containing red blood cells. Between these channels there was a fibrous connective tissue. The patient was well seven years later at the time the report was made.

The second patient, a man, aged thirty, complained of hematuria and pain in the left groin and burning on urination. He had had one attack of hematuria eight years before, which had cleared up within several days not to recur again until ten days before his admission. There was tenderness on the left side about half way between the umbilicus and the anterior superior iliac spine. There were no kidney masses or tenderness. The voided specimen of urine contained blood cells. Cystoscopic examination showed that the left ureter was discharging blood. A pyelogram showed a markedly flattened middle calyx. A left nephrectomy was performed. At operation there was a marked adherent portion about the center of the kidney on the dorsal surface, the size of a silver dollar. There was also some depression



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and discoloration. In the medulla, near the pelvis, there was a reddish hemorrhagic area, which histologically consisted of larger and smaller closely packed dilated venous sinuses, filled with blood. Sections of the retracted areas showed what appeared to be an infarction, with collapse of the parenchyma, distorted blood channels and cellular infiltration and fibrosis. The diagnosis was cavernous hemangioma.

Hemangioma of the kidney is rare, is usually single but may be multiple. These may be situated in the pelvis, medulla, or cortex although they are seldom observed in the cortex. Pathologic study of these specimens show them to be composed of large cavernous sinuses lined with endothelium and filled with blood. Hematuria is the only constant symptom and injury may play a part in its onset. Clinical symptoms arise from hemorrhage and are due to ulceration into the pelvis of the thin-walled vessels. Preoperative diagnoses are seldom made. Many cases were considered as essential hematuria. Jacobs and Rosenberg,<sup>7</sup> also Jenkins and Drennan,<sup>9</sup> claim that the pyelogram presents a mottled appearance due to the permeation by the pyelographic medium of the angiomatous spaces, and the interpretation is difficult because of blood clots in the pelvis.

Renal stones, by reason of chronic irritation, are said to be provocative agents in the etiology of cancer of the kidney pelvis. Martin and Mertz<sup>15</sup> collected 108 cases of renal malignancy associated with renal stones. The average duration of symptoms of carcinoma was five months in this series of cases. Squamous cell carcinomas are said to be associated with kidney stones quite frequently. Scholl and Foulds<sup>22</sup> in 1925 reported 5 cases of squamous cell carcinoma of the renal pelvis, 4 of which were associated with renal stones. One of these patients gave a history of intermittent kidney colic and hematuria for twelve years preceding the cancer. Wells<sup>25</sup> collected 11 cases in 1922, six of which were associated with urinary stones. Scholl<sup>21</sup> reported 2 additional cases in 1933. These cases will be abstracted briefly. A woman, aged fifty-seven, had had kidney stones for seven years. The left kidney was removed and showed a squamous cell carcinoma. The kidney contained many small tumors and many large nodules, measuring 3 to 4 cm. in diameter. This patient died two months later with metastases to the lungs, liver, pancreas and retroperitoneal lymph nodes. The right suprarenal gland had been replaced by the tumor. Scholl's second patient was a woman, aged sixty-seven, who had suffered from thyroid disease since the age of twelve. For two years before admission she had noticed a gradually enlarging mass in her left abdomen which was associated with pain. Physical examination revealed a large palpable mass in the left abdomen and the roentgenogram showed stones and a large calcified mass in the lower kidney pole. An attempted pyelogram showed the iodide solution interrupted at the cal-

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cific area near the lower edge of the mass. Operation was performed and the kidney contained pus and stones. There was a squamous cell carcinoma of the renal pelvis which had extended into the surrounding structures too extensively to be removed.

The prognosis in cases of squamous cell tumor is poor. Four of the 5 patients reported by Scholl and Foulds died during the first four months, and one was alive six months after operation. Metastases develop early and extensively and the condition is rapidly fatal.

In the Cleveland Clinic series of 23 confirmed cases of carcinoma of the kidney there were 3 squamous cell or epidermoid carcinomas. One of the patients gave a history of passing calculi. The two other histories did not suggest a previous renal infection or stones. These 3 cases are presented briefly.

The first patient, a woman, aged forty-one, was first observed in August, 1924. She had noticed a mass in her right side in October, 1923. A roentgenographic examination at that time showed a large mass in the right abdomen but no stone shadows. One week before admission to the Clinic she had had chills, fever, and pain in the right abdomen which was followed by the passing of calculi and hematuria.

Physical examination revealed a large, tender, nodular mass in the right kidney region, and much pus and blood were found in the urine. The roentgenogram of the kidney, ureters, and bladder showed a greatly enlarged right kidney which was interpreted as a tumor and the cystoscopic examination revealed a cauliflower-like growth in the region of the right ureteral orifice. The ureteral orifice could not be identified and neither urine nor intravenously injected dye could be seen coming from this region. The right kidney function (estimated from the bladder urine with a catheter to left kidney pelvis) was 10 per cent, the left kidney function was 36 per cent.

Operation was undertaken, but the mass was of such huge size and was so adherent to the surrounding structures that removal was impossible. The patient died in the hospital one month later. Post-mortem examination of the right kidney showed the kidney to be five or six times the normal size. The capsule was extremely thick and adherent. There was invasion through the capsule which extended down the ureter and also involved the retroperitoneal lymph nodes, the under surface of the diaphragm, and the liver. Palpation of the bladder did not reveal any tumors and there was only slight involvement of the ureter near the bladder. There was extensive malignant invasion in the region of the duodenum and the pancreas. The pelvis of the kidney was tremendously dilated and was filled with necrotic material, but contained no stones. The central portion of the kidney showed marked degeneration and hemorrhage. Microscopic examination disclosed deeply chromatic stratified squamous epithelial cells growing in

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wild profusion in every direction and infiltrating deeply. Practically all the renal parenchyma had been destroyed. Pearl formations, degenerating and metaplastic cells were seen in great abundance. The diagnosis was squamous cell carcinoma of the kidney probably arising in the renal pelvis.

The second patient was a man, aged fifty-two, who was admitted to the Clinic on April 14, 1933, complaining of pain in the back, blood in the urine and nocturia, which had persisted for ten weeks. There was no history of previous genitourinary trouble or the passage of calculi.

The physical examination revealed a movable tumor in the right kidney region. Laboratory examinations showed numerous red and white blood cells in the urine and an increase of urea in the blood. A roentgenogram of the chest showed no evidence of metastasis. Considerable bladder trabeculation was apparent on cystoscopic examination and the specimen collected from the right ureter was bloody. The pyelogram showed marked compression and infiltration of the upper three-fourths of the kidney. This was interpreted as carcinoma of the kidney.

The patient was given a complete course of preoperative roentgen therapy and a right nephrectomy was performed April 28, 1933. The kidney was slightly enlarged but normal in contour. On the anterior surface of the kidney and extending out from the hilum was a bulging tumor measuring 7.5 by 6 cm. The upper half of the kidney cortex was considerably scarred. A few cortical cysts were present. The tumor had infiltrated and replaced the hilar and peripelvic fat and had sent branches up between the pyramids. It was not well circumscribed and diffusely infiltrating. There were no stones present. A large branch of the renal artery was infiltrated and occluded by the tumor.

Various sections through the kidney pelvis showed normal pelvic mucosa, complete loss of mucosa, metaplastic changes, ulcerated mucosa, and replacement of the mucosa by an infiltrating squamous cell carcinomatous growth. The tumor was diffusely infiltrating outward from the renal pelvis into the surrounding medulla, cortex and the peripelvic fat. There was marked atrophy and fibrosis of the kidney tissue and involvement of the renal vein and artery, both infiltration and thrombi. The microscopic diagnosis was squamous cell carcinoma of the right kidney originating in the pelvis.

The patient's convalescence was uneventful. One month after operation he reported for observation. He looked well, had a wonderful appetite, and had gained 6½ pounds. One month later he looked well but had begun to feel a little weak. Four months after operation a roentgenogram of the chest showed definite metastases, and the patient is now declining rapidly.

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The third patient is a man, aged fifty-four, who presented himself on November 11, 1932, complaining of pain in the back and right hip, and blood in the urine. These symptoms had been present for three months. There was no history of previous kidney disease.

Physical examination revealed a small mass in the right kidney area and definite cachexia. There was a small amount of microscopic blood in the urine and an occasional pus cell. Cystoscopic examination showed no function from the right kidney with compensatory function of the left kidney. Both the pyelogram and the urogram were unsatisfactory for diagnostic purposes.

The preoperative roentgenograms of the chest and pelvis showed no evidence of metastases.

Right nephrectomy was performed on November 11, 1932. The kidney was densely adherent everywhere but particularly at the upper pole. The renal vein contained a thrombus of tumor tissue. The kidney removed was not enlarged nor deformed. There were a few small cortical cysts and the fetal lobular markings were fairly distinct. The pelvis was moderately dilated, the mucosa was rough and had small papillary-like projections. The peripelvic tissue was infiltrated with tumor tissue. All hilar structures were invaded by the tumor tissue, and the cortex and medulla were diffusely infiltrated. The ureter was stenosed. The renal artery and vein and the kidney capsule and perinephric fat were involved by the tumor.

Microscopic examination showed a thickened, somewhat papilliferous pelvic surface covered by single and multiple layers of rather large, atypical, epithelial cells, having an epidermoid appearance, but without keratinization. Extending outward from the pelvis, there were solid masses of epithelial cells of similar type diffusely infiltrating the medulla, cortex and capsule proper of the kidney. There was extensive fibrosis of the renal tissue. There was similar infiltration of the fatty extrarenal tissue.

In less than one month after operation, metastases were demonstrated in the upper ends of the femurs. These areas did not show bone changes before operation, but undoubtedly the pain which the patient complained of on admission was caused by metastases which could not be demonstrated at that time on the roentgenogram. These distant metastases occurred in less than four months after the first symptom.

The clinical course and the pathology in these 3 cases parallels the course of squamous cell carcinoma as described in the literature. This lesion is rapidly fatal and the prognosis is gloomy indeed.

## SUMMARY

A general review of various aspects of the problem of roentgenologic diagnosis of renal tumors is presented, in which the relative merits of

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retrograde and excretory urography are discussed. Pneumopyelography, with its advantages and dangers, is reviewed.

The controversy regarding pathologic classification is cited, with some of the reasons for these difficulties.

Certain problems relating to the diagnosis of renal lesions presenting themselves in clinical practice are mentioned and illustrated by case reports from the literature and the files of the Cleveland Clinic.

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## THE DIFFERENTIAL DIAGNOSIS OF CORONARY ARTERY DISEASE

### Diseases Which Simulate Angina Pectoris and Coronary Thrombosis

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During the past 15 years, there has been a progressive increase in the frequency with which the diagnosis of coronary thrombosis or angina pectoris has been made. This increase has resulted in part from an absolute increase in the incidence of coronary artery disease and in part from widespread diffusion of knowledge concerning its clinical features. In the great majority of cases, the presence of angina pectoris or coronary thrombosis is correctly recognized, but as a result of the popularity of these diagnoses, other diseases with similar symptoms undoubtedly are being included at times under the same classifications. Although such errors are not common, they are of importance because of their bearing upon prognosis and treatment. It is the purpose of this communication to review certain recent experiences in which other conditions were confused with or closely simulated coronary artery disease and to point out the significant features in the history and clinical findings upon which a correct diagnosis was, or might have been, established.

#### UPPER ABDOMINAL DISEASE

Early writers<sup>1,2</sup> on coronary thrombosis directed attention to the fact that the disease might closely simulate acute surgical conditions in the upper abdomen, and the possibility of erroneously attributing the symptoms of coronary occlusion to upper abdominal disease has since been emphasized repeatedly. More recently, a few observers have pointed out the possibility that errors may be made in the reverse direction and have reported cases in which symptoms due to gall-bladder disease or perforated peptic ulcer suggested coronary artery disease.<sup>3,4,5</sup> In the first of the two following case reports, symptoms due to cholelithiasis were attributed originally to coronary occlusion, while in the second, an esophageal hiatus hernia caused symptoms simulating angina pectoris.

**Case 1. Cholelithiasis with Pain Suggesting Coronary Thrombosis.** A white, single woman, aged 35 years, was referred to the Clinic on April 11, 1935, with a diagnosis of coronary thrombosis. Four days earlier, severe pain had developed suddenly in the interscapular region while the patient was working at her desk. This pain was followed almost immediately by agonizing burning pain in the lower substernal region which radiated upward toward both shoulders and into the epigastrium and both upper abdominal quadrants. The pain was of such severity that the patient was unable to remain quiet. Walking and change in position had no effect. There was moderate dyspnea, and the patient noted that any attempt to take a deep breath increased the dis-



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comfort. Nausea developed soon after the onset, and the patient induced vomiting on three occasions but without relief. After four hours, she called her physician, who administered morphine. The pain subsided gradually during the next two hours, but a feeling of soreness was still present over the lower chest and epigastrium four days later. No jaundice had been noted, and the urine had remained of normal color. The past history was irrelevant except for the fact that during the preceding six months there had been three attacks of moderate epigastric pain associated with pain in the interscapular area. On each occasion, the symptoms had developed about one hour after eating and had been relieved in about ten minutes by taking soda and belching.

Physical examination revealed a moderately obese individual with no cyanosis or jaundice. The pupils reacted normally. The heart was not enlarged, and its rhythm and rate were normal. A faint systolic murmur was heard over the apex. There was no friction rub, and the heart sounds were of good quality. The blood pressure was 120 mm. systolic and 82 mm. diastolic. The lungs were clear. Slight tenderness was present in the epigastrium and below the costal margin in the right anterior axillary line. There was no peripheral edema. The temperature by mouth was 99.4°F.

The leucocyte count was 10,500 per c.mm. The urine was normal. The icteric index was 8. An electrocardiogram with a precordial lead in addition to the three conventional leads showed no abnormalities. Roentgenograms of the chest revealed no evidence of pathology in the heart, lungs or aorta.

Because of the patient's age, the occurrences of pain in the interscapular region, the normal electrocardiographic findings and the history of earlier, milder attacks not suggestive of coronary disease, it was concluded that the symptoms had not resulted from coronary thrombosis. Cholecystograms were advised. The gallbladder was not visualized but a single large calcium type stone was seen in the gallbladder area (Fig. 1).

Cholecystectomy was performed on May 1, 1935. The gallbladder contained a single spherical stone, 1.7 cm. in diameter. The patient has had no recurrence of symptoms.

### Case 2. *Esophageal Hiatus Hernia Simulating Angina Pectoris.*

A white, single woman, aged 72 years, had experienced a sensation of fullness and pressure high in the epigastrium at irregular intervals for one year. The discomfort usually developed after the evening meal and was relieved in 20 to 30 minutes by drinking hot water and belching. Shortly after the first appearance of these symptoms, the patient began to experience attacks of numbness and severe aching pain over the top of the left shoulder, extending down the left arm for a variable distance. These symptoms likewise developed in the evening, but at first, the patient did not associate them with the abdominal discomfort. After a few weeks, however, she noted that the shoulder and arm pain always was accompanied by epigastric distress, although at times epigastric distress occurred without other symptoms. As in the case of the epigastric discomfort, drinking hot water and belching gave relief from the shoulder and arm pain. Neither type of pain was precipitated by exertion, although on a few occasions all symptoms had been brought on by bending forward acutely. For three or four years, the patient had experienced moderate dyspnea on walking rapidly, and six months before examination, she had been told her blood pressure was elevated.

Physical examination revealed a moderately obese individual. The left border of cardiac dulness was 1 cm. beyond the mid-clavicular line in the

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FIGURE 1, CASE 1.—Large gall stone in non-functioning gallbladder.

fifth intercostal space. The aortic second sound was moderately accentuated, and a short systolic murmur was heard over the apex and aortic area. The rate and rhythm were normal. There was moderate, diffuse thickening of the peripheral arteries, and the blood pressure was 160 mm. systolic and 84 mm. diastolic. The percussion note was dull over the base of the left lung up almost to the angle of the scapula, and the breath sounds and voice transmission were suppressed over this area. A moderate number of medium moist râles were heard over the base of both lungs. Abdominal examination was negative. There was no peripheral edema.

Examination of the blood and urine gave normal results. An electrocardiogram revealed nothing abnormal except for moderate left axis deviation.

Although the type of pain was suggestive of angina pectoris, there were certain features in the symptomatology which argued against the acceptance of

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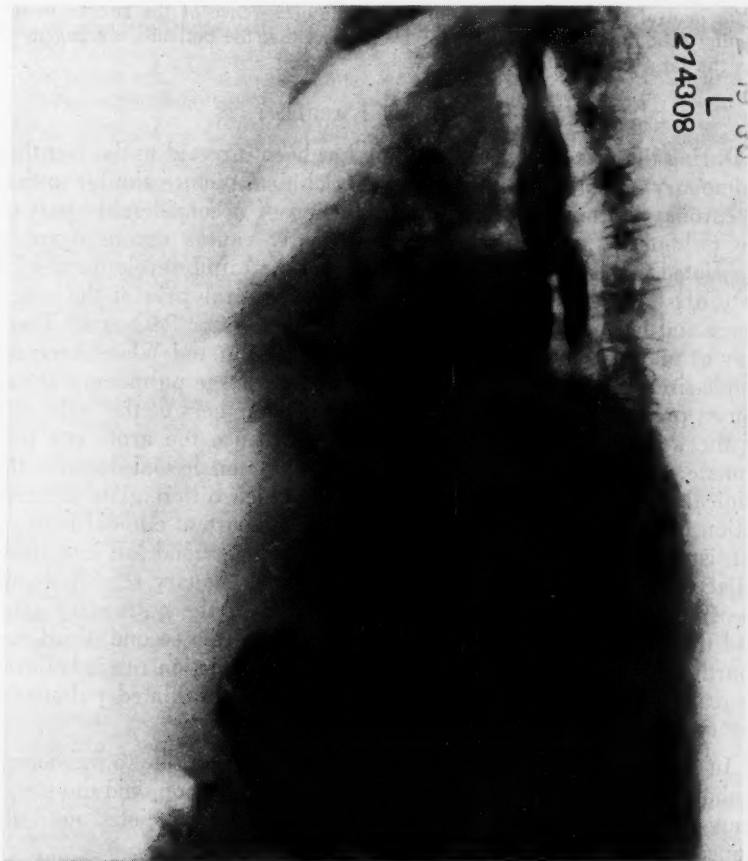


FIGURE 2, CASE 2.—Esophageal hiatus hernia with approximately two-thirds of stomach lying above the diaphragm. Lateral view.

this diagnosis. The most important of these were the lack of relationship between the attacks and exertion, the prompt relief experienced after drinking hot water and belching, and the fact that although the abdominal pain had been situated high in the epigastrium, there had at no time been radiation to the substernal region. It therefore was decided to investigate the gastro-intestinal tract. Roentgenologic examination after the administration of a barium meal revealed a large diaphragmatic hernia of the esophageal hiatus type with approximately two-thirds of the stomach lying above the diaphragm (Fig. 2). The herniation of the stomach was constant with the patient in all positions, and there was no retention of barium at the end of four hours. The esophagus appeared to be of normal length. Undoubtedly the epigastric pain resulted from distention by gas of the portion of the stomach lying above the diaphragm, while the pain over the left shoulder and in the left arm was due to irritation

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of the central tendon of the diaphragm. The occurrence of the attacks in the evening probably was accounted for by the fact that the patient's evening meal was the largest of the day.

#### PULMONARY EMBOLISM

During the past few years attention has been directed to the fact that pulmonary embolism may give rise to a clinical picture similar to that of coronary thrombosis. Sudden occlusion of a considerable part of the pulmonary circulation characteristically causes severe dyspnea associated with retrosternal oppression and the rapid development of a state of shock. There may or may not be pleural pain at the onset. Fever and leucocytosis usually appear within the first 24 hours. There may or may not be blood-tinged sputum. McGinn and White<sup>6</sup> recently emphasized the fact that sudden occlusion of a large pulmonary artery causes prompt dilatation and failure of the chambers of the right side of the heart and termed this cardiac disturbance the acute cor pulmonale. They report 9 cases of acute cor pulmonale and describe the clinical and electrocardiographic features which differentiate the condition from coronary thrombosis. The most important clinical features consist of an increased pulsation palpable in the second left interspace adjacent to the sternum, accentuation of the pulmonary second sound, the frequent occurrence of a gallop rhythm over the pulmonary area, and the occasional presence of a friction rub in the second, third and fourth interspaces adjacent to the sternum. The friction rub is believed to result from irritation of the pericardium by the dilated pulmonary artery and right ventricle.

In the case which follows, the symptoms, although due to pulmonary embolism, were highly suggestive of coronary occlusion, and the significance of certain of the physical signs was not appreciated until the appearance of the report of McGinn and White.<sup>6</sup>

##### Case 3. *Pulmonary Embolism Simulating Coronary Thrombosis.*

A white man, aged 65 years, who was known to have had chronic nonspecific prostatitis for several years, was admitted to the hospital on April 21, 1933, because of pain in the left lower chest posteriorly. The pain was increased by deep breathing and was accompanied by dyspnea and an unproductive cough. The symptoms had developed suddenly two days earlier.

Physical examination revealed dullness over the base of the left lung together with a faint pleural friction. The heart was not enlarged; its rhythm was regular, and no murmurs were heard. The aortic second sound was louder than the pulmonary second. The temperature by mouth was 100.4°F., the pulse rate, 96 per minute, and the blood pressure, 126 mm. systolic and 70 mm. diastolic. Roentgenologic examination of the chest showed a large area of consolidation in the lower lobe of the left lung. A diagnosis of pulmonary infarction was made. On the second day after admission, the patient began to raise blood-streaked sputum, and on the following day, he complained of pain over the inner aspect of the left thigh, approximately along the course

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of the great saphenous vein. It was concluded, therefore, that the patient had pelvic thrombophlebitis with extension to the femoral and great saphenous veins on the left. The pelvic thrombophlebitis presumably was the source of the pulmonary embolus.

The patient improved gradually until the thirteenth day after admission. At that time, after three days of normal temperature, he experienced sudden, constricting pain in the retrosternal region and over the left anterior chest. The pain was accompanied by dyspnea, orthopnea, restlessness and great apprehension. The pulse rate increased to 116 per minute and the blood pressure dropped to 106 mm. systolic and 60 mm. diastolic. The temperature rose to 101° F. within six hours and during the following four days ranged between 100° and 103° F. On the day after the appearance of these symptoms, examination revealed accentuation of the pulmonary second sound and a pericardial friction rub over the third and fourth intercostal spaces adjacent to the sternum. A few fine râles were present over the lung bases. The patient's color was of a dusky ashen hue. The leucocyte count was 14,100 per c.mm. The sputum was streaked with blood.

A diagnosis of extensive pulmonary embolism was made, and undoubtedly, this condition resulted in the development of the acute cor pulmonale of McGinn and White.<sup>6</sup>

The patient's condition was extremely serious for nearly 48 hours. He was kept in an oxygen tent, and morphine was administered subcutaneously on several occasions. The friction rub persisted for approximately 36 hours. The subsequent clinical course was uneventful, and the patient was discharged from the hospital six weeks later.

## DISSECTING ANEURYSM OF THE AORTA

Dissecting aneurysm of the aorta gives rise to a symptom complex which closely resembles that of acute coronary occlusion. The condition is characterized by the sudden onset of severe pain in the anterior chest, often radiating to the back and legs, and usually described by the patient as crushing or tearing in quality. The pain usually lasts for 48 hours or longer and frequently is present to a greater or lesser degree until death occurs. At the onset, repeated injections of morphine give only partial and gradual relief. Fever and leucocytosis usually develop within 24 hours of the onset.

White, Badger and Castleman<sup>7</sup> recently have discussed the differential diagnosis of dissecting aortic aneurysm and coronary thrombosis. They direct attention to the fact that in dissecting aneurysm, the severe pain is abrupt in onset in contrast to its more gradual evolution in coronary occlusion. The frequent radiation of the pain to the back and legs also is of diagnostic importance. Particular emphasis is placed, however, upon the maintenance of hypertension throughout the acute illness, the lack of diminution in the quality of the heart sounds and the absence of coronary T-waves in repeated electrocardiograms.

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The following case, in which an erroneous diagnosis of coronary thrombosis was made, illustrates how closely dissecting aortic aneurysm may simulate coronary occlusion.

**Case 4. Essential Hypertension; Syphilitic Aortitis with Aneurysm of the Aorta; Dissecting Aneurysm of the Aorta with Rupture into the Left Pleural Cavity.** The patient, a white man, aged 58 years, had known of the presence of hypertension for six years and for the same length of time had been receiving conservative treatment for syphilis. On September 14, 1934, three days before admission to the hospital, severe crushing pain had developed suddenly in the lower left chest anteriorly. The pain did not radiate, and in spite of repeated doses of morphine sulphate, it was not entirely gone at the time the patient entered the hospital. There had been no definite dyspnea, but the patient had vomited several times during the first 12 hours of the illness and had been mentally confused from the onset.

At the time of admission to the hospital, the temperature by mouth was 100.4°F., the pulse rate, 100 per minute, and the blood pressure, 190 mm. systolic and 110 mm. diastolic. There was no cyanosis. The pupils reacted normally. The left border of cardiac dullness was 12 cm. from the midsternum in the sixth intercostal space. No increased dullness could be made out over the base of the heart. The cardiac rhythm was regular, and the sounds were of good quality. The aortic second sound was greater than the pulmonary second. A moderate systolic murmur was present over the apex. There was advanced sclerosis of the peripheral arteries. The lungs were clear. Abdominal examination gave normal findings. The tendon reflexes were brisk and equal.

The leucocyte count was 11,400 per c.mm. The urine contained a heavy trace of albumin, and microscopic examination of the sediment revealed a few white blood cells and an occasional hyaline cast. The Wassermann reaction of the blood was 4 plus. Electrocardiograms taken on the day of admission and two days later showed slight inversion of the T-wave in Lead I and moderate left axis deviation.

Shortly after the patient entered the hospital, the pain increased greatly in severity for a period of two hours. Gradual relief was obtained with one-fourth grain of morphine sulphate subcutaneously. On the evening of the fourth day after admission, severe pain again developed suddenly in the left lower chest and was accompanied by pallor, profuse perspiration and a rise in pulse rate to 124 per minute. One-fourth grain of morphine sulphate was given subcutaneously without relief, but after a similar dose 20 minutes later, the patient gradually became more comfortable. On the following day, he remained free from pain, but that night, shortly after midnight, he awakened restless and confused, and while attempting to get out of bed, suddenly died.

During the first three days in the hospital, the blood pressure ranged between 190 mm. and 210 mm. systolic and 110 mm. and 136 mm. diastolic. It then dropped rapidly and on the day before death, was 146 mm. systolic and 90 mm. diastolic. The leucocyte count reached a maximum of 12,600 on the second day after admission and then decreased to 8,200 on the fourth day after admission.

**Necropsy.** When the thorax was opened, the left lung was found to be compressed by a large postmortem clot which weighed 1,500 grams. About 300 cc.



## THE DIFFERENTIAL DIAGNOSIS OF CORONARY ARTERY DISEASE

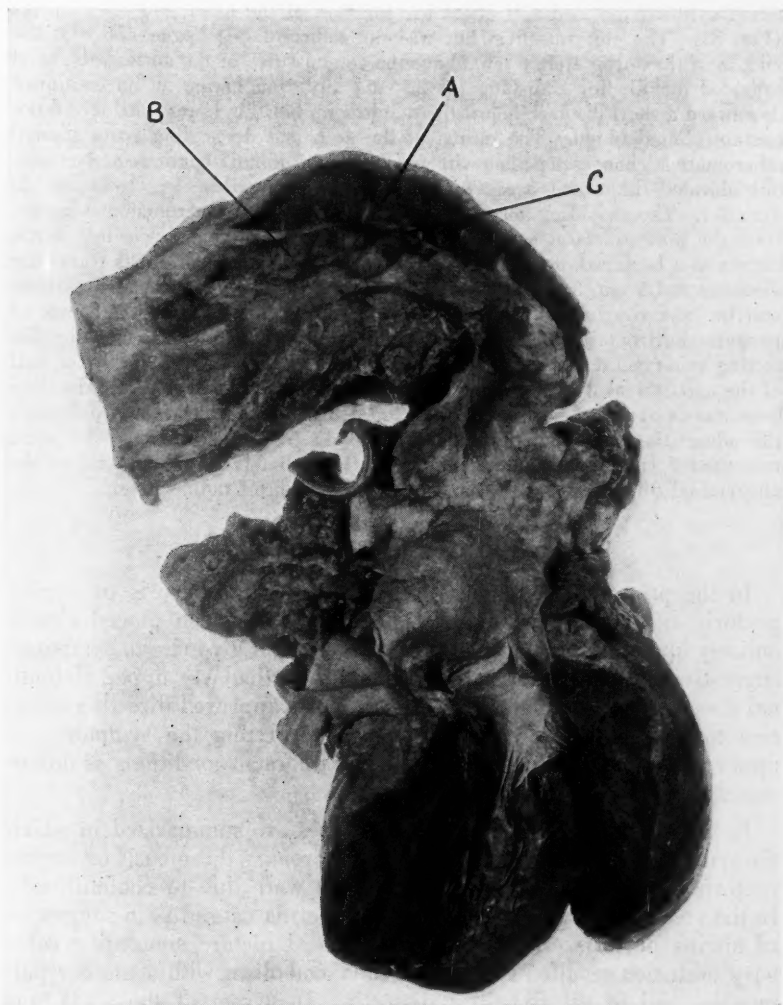


FIGURE 3, CASE 4.—Dissecting aneurysm of the aorta. The dissecting aneurysm containing the blood clot is shown at A and the aneurysmal dilatation at B. The laceration in the intima cannot be seen but is situated at C.

of unclotted blood also were present. The arch and upper portion of the descending aorta appeared to be greatly dilated. The pericardium was normal. The heart weighed 570 grams, and the walls of both ventricles were increased in thickness. The coronary arteries were patent throughout.

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Upon opening the aorta, a large blood clot, 1 to 3 cm. in thickness, was found splitting the media at about the junction of the inner and outer halves (Fig. 3). The clot was firm but was not adherent. It began above at the middle of the aortic arch, 8 cm. above the commissures of the aortic valve, and extended distally for a distance of 22 cm. Splitting of the media continued downward a short distance below the diaphragm, but this lower portion did not contain clotted blood. The intima of the arch and descending aorta showed atheromatous changes together with patchy, longitudinal striations and numerous elevated, indurated areas ranging from a few millimeters to 2 cm. in diameter. The ascending aorta showed only a few small atheromatous plaques. Over the postero-lateral aspect of the upper portion of the descending aorta, there was a localized aneurysmal dilatation measuring 3.5 cm. in its transverse diameter and 9 cm. longitudinally. The intima in this area presented extreme scarring and roughening, and at the upper margin of the area there was an irregular horizontal laceration, 2 cm. long, which communicated with the dissecting aneurysm. Externally, the left lung was adherent over the upper half of the aneurysmal dilatation, and just below the lower limit of these adhesions there was an irregular, horizontal laceration, 1.5 cm. long, which extended through the adventitia and communicated with the dissecting aneurysm. The aorta measured 7 cm. in internal circumference immediately above and below the aneurysmal dilatation, and 10 cm. at the midportion of the aneurysm.

#### SUMMARY

In the past, in discussions of the differential diagnosis of angina pectoris and coronary thrombosis, emphasis has been placed almost entirely upon the fact that these conditions might give rise to symptoms suggestive of some other pathologic state, particularly upper abdominal disease. Only of late have a few reports appeared directing attention to the possibility of erroneously interpreting the symptoms of upper abdominal disease and certain intrathoracic conditions as due to coronary artery disease.

In the present communication, four cases are summarized in which the symptoms closely resembled those of coronary thrombosis or angina pectoris. In the first case the symptoms were due to cholelithiasis. In the second, a large esophageal hiatus hernia caused pain suggestive of angina pectoris. In the third, a clinical picture simulating coronary occlusion resulted from pulmonary embolism with acute cor pulmonale, and in the fourth, a dissecting aneurysm of the aorta was mistakenly diagnosed coronary thrombosis. The cases illustrate the diagnostic significance of negative electrocardiographic findings and also indicate the importance of detailed analysis of the patient's symptoms and physical signs. In the future, diaphragmatic hernia, upper abdominal disease, dissecting aneurysm of the aorta and pulmonary embolism with acute cor pulmonale should be excluded before a diagnosis of angina pectoris or coronary thrombosis is made in patients presenting features not typical of coronary artery disease.

## THE DIFFERENTIAL DIAGNOSIS OF CORONARY ARTERY DISEASE

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## URETERAL TRANSPLANTATION FOR EXSTROPHY AND CARCINOMA OF THE BLADDER

CHARLES C. HIGGINS, M.D.

Exstrophy of the bladder is one of the most unfortunate and pathetic of all congenital anomalies. According to the statistics of Neudörfer,<sup>1</sup> it occurs approximately once among every 50,000 births and it is stated that 50 per cent of the children who have this anomaly die before they attain the age of ten years, and that 66 per cent die before the twentieth year, unless relief is afforded by surgical intervention.

The late Dr. Robert C. Coffey deserves the gratitude of the profession for his valuable contributions in the development of the operation for the transplantation of the ureter into the recto-sigmoid. In 1911 he<sup>2</sup> emphasized the importance of utilizing the valve principle in this operation, and the basis for this contribution was afforded by observations of the anatomical relationships of the common bile duct in its course through the walls of the duodenum. Dr. Coffey noted that this duct courses through the muscularis and then between the muscularis and mucosa of the duodenum for some distance before it opens into the lumen of the duodenum itself.

Since the adoption of the valve principle in the transplantation of the ureters, the operation has been performed frequently and has been accepted as a sound and justifiable surgical procedure. Dr. Coffey, however, stated two objections to the procedure which have prevented its general acceptance by surgeons. The first was that it is impossible to maintain uninterrupted kidney function and not alter the normal physiologic processes of the upper urinary tract when both ureters are transplanted simultaneously. In the second place, the danger of infection always has been great and is the most common cause of death, regardless of the surgical technique employed.

In 1933, I described a technique by which both ureters could be transplanted simultaneously without interruption of renal function.<sup>3</sup> By this method the continuity of the ureter remains intact until a new channel has been established, and the normal passage of urine from the kidney through the ureters and into the bladder is not disturbed until it is diverted through the newly established communication. In addition, since the lumen of the bowel is not exposed, the danger of infection is negligible. Since both ureters can be transplanted simultaneously, the length of time required for hospitalization is reduced materially. Another advantage is that the procedure is accompanied by only slight postoperative reaction.

By this technique, a child with exstrophy of the bladder may be operated upon much earlier in life before hydro-ureter, hydronephrosis and associated renal infection and impairment of renal function

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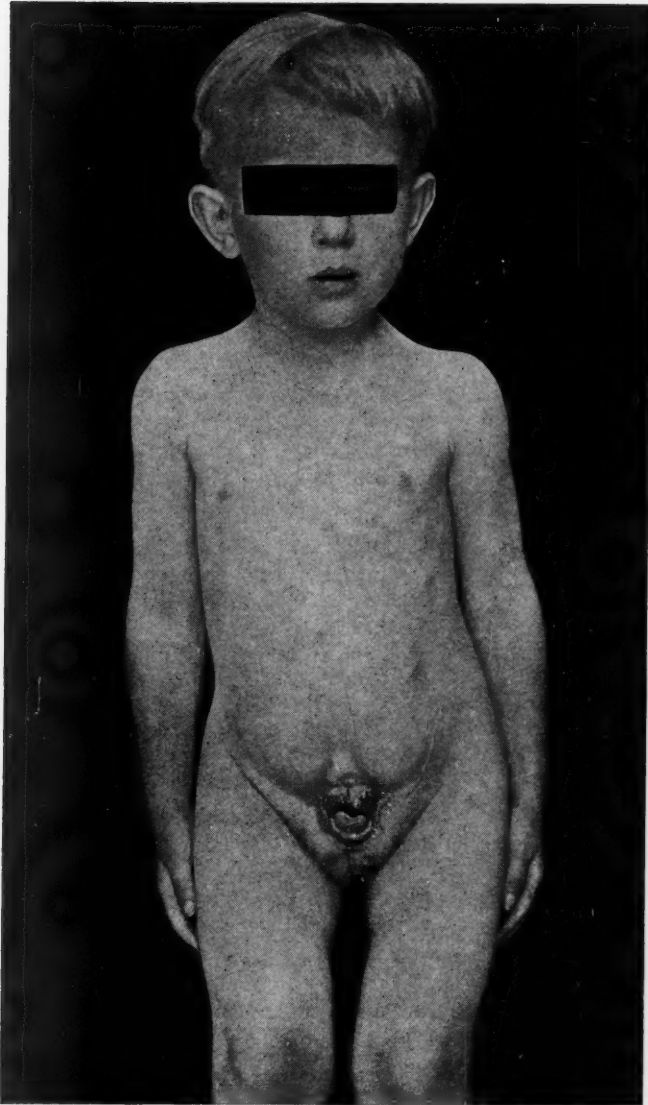


FIGURE 1.—Photograph of patient showing exstrophy of the bladder.

have appeared. If the tone of the rectal sphincter is adequate, the sooner surgical intervention is employed, the less likelihood is there that irreparable renal damage will have taken place.

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FIGURE 2.—Urogram taken by intravenous method preoperatively showing good function of both kidneys. There is no evidence of hydronephrosis or hydro-ureter.

The following is an illustrative case:

**History**

A boy, aged 4 years, came to the Clinic after a diagnosis of exstrophy of the bladder had been made by his physician. Since his birth the parents had noted the abnormal position of the bladder, the constant soiling of the child's



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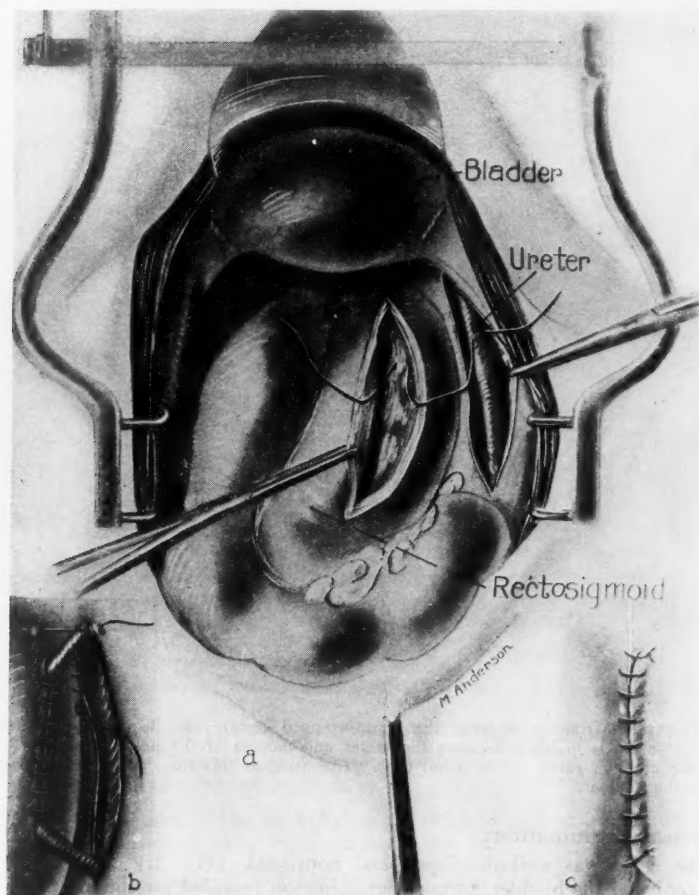


FIGURE 3.—Drawing showing (a) transfixion suture placed between the ureter and mucosa of the recto-sigmoid; (b) muscularis and serosa layers reapproximated over the ureter; (c) suture of posterior parietal peritoneum over the line of incision in the bowel.

clothing and irritation of the adjacent skin from the urine. There had been no apparent difficulty in the control of the bowels. The child began to walk at the age of twelve months and to talk when he was fifteen to eighteen months old. When he was two years old a bilateral inguinal herniorrhaphy had been performed. For a few months, bleeding from the raw surface of the bladder had occurred frequently. No other abnormalities had been observed.

The father and mother were both living and well and one brother was living and free from congenital abnormalities.

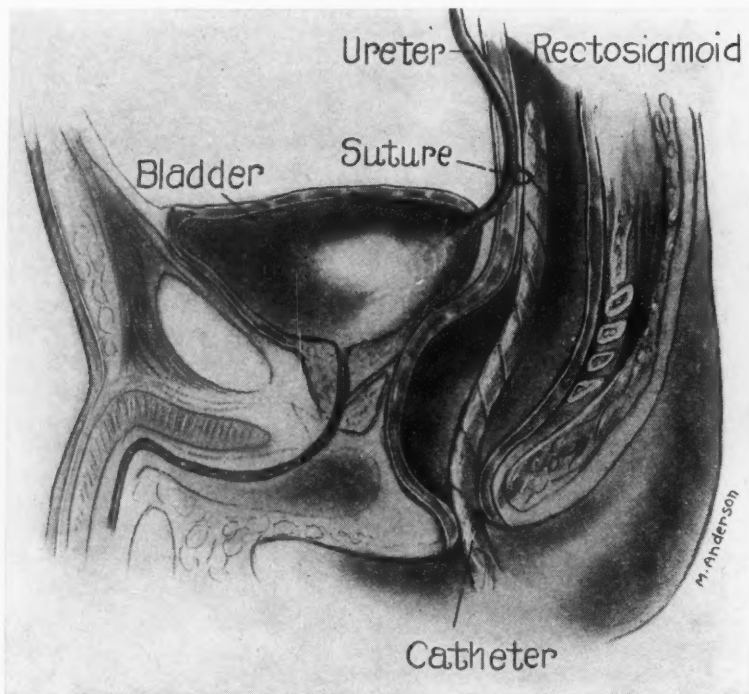


FIGURE 4.—Drawing showing the gauze-wrapped rectal tube in place. The transfixion suture is in place between the ureter and mucosa of the bowel which includes a bite into the gauze of the rectal tube. The urine at this time passes uninterrupted into the bladder.

#### Physical Examination:

The child was well developed and nourished. (Fig. 1.) Except for the exstrophy of the bladder, physical examination revealed no abnormalities. At the lower part of the exstrophic bladder, urine could be seen spurting from the ureteral orifices. Epispadias also was present. The incision from the previous operation was well healed, and there was no evidence of recurrence of the hernia. The testicles were normal and had been placed in the scrotum at the time the herniorrhaphy had been performed.

#### Laboratory studies:

A roentgenogram of the genito-urinary tract showed normal findings. An intravenous urogram made after the intravenous injection of skiodan (Fig. 2) showed good function of both kidneys with no evidence of hydro-ureter, hydronephrosis or stasis. Examination of specimens of urine secured from the kidney pelvis by catheterization gave no abnormal findings. A function test (5 cc. of indigo carmine injected intravenously) showed that the dye spurting from the right ureteral orifice in four minutes with 4 + concentration and from the left in a similar length of time. Examination of the blood

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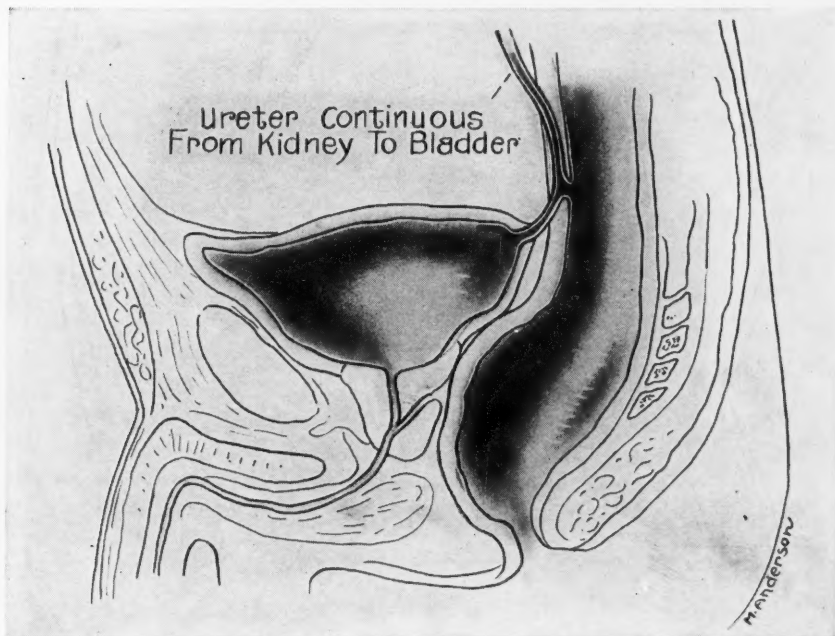


FIGURE 5.—Drawing showing new communication between the ureter and bowel established. Rectal tube and sutures have been passed.

showed 4,370,000 red blood cells, 9,800 white blood cells and 80 per cent hemoglobin. The Wassermann reaction was negative. The blood urea was 28 mg. per hundred cubic centimeters.

The child was admitted to the hospital and a bilateral transplantation of the ureters into the rectum was performed three days later.

### Operative technique:

Under ether anesthesia, a number 18 French catheter, wrapped with a layer of vaseline gauze, was inserted into the rectum and one ounce of methiolate solution was introduced into the recto-sigmoid through the catheter. A small rubber apron was then secured to the lower abdominal wall in such a way as to isolate the extrophy of the bladder from the operative field. A low mid line incision was made and carried through the peritoneum. The intestines then were displaced into the upper abdominal cavity and held in place by moist tapes. The right ureter was isolated at the usual site of transplantation. After incision of the posterior peritoneum, the ureter was delivered from its bed and mobilized for approximately two inches. A suitable site adjacent to the mobilized ureter was selected in the recto-sigmoid and a longitudinal incision one and one-half inches in length was made through the serosal and muscularis layers to the mucosa. These layers then were undermined by blunt dissection.

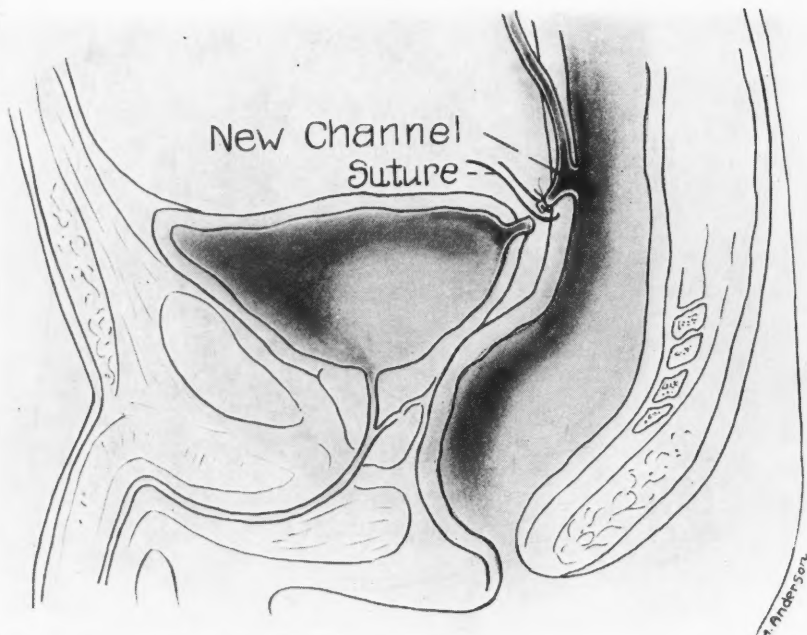


FIGURE 6.—Drawing showing the continuity of the ureter severed at the point of emergence from the trough and additional anchoring suture in place.

The ureter was placed in the trough of the bowel thus formed. A silk mattress transfixion suture was passed through the lumen of the ureter, then through the mucosa of the recto-sigmoid and included a bite into the gauze surrounding the rectal tube. The suture was tied quite tightly. The transfixion suture between the ureter and the bowel was placed at the lower end of the incision in the recto-sigmoid in order that a blind pouch of ureter would not be left when the continuity of the ureter was interrupted. The muscularis and serosal layers were reapproximated over the ureter with interrupted silk sutures. The outer edge of the posterior peritoneum was sutured over the incision in the bowel with interrupted silk sutures, thereby placing the anastomosis in the retroperitoneal position and immobilizing the recto-sigmoid. (Figs. 3-7.)

A similar procedure was performed on the left ureter and bowel. The abdomen was closed in layers without drainage.

#### Postoperative course:

The rectal tube with the two sutures between the ureters and the recto-sigmoid were passed in sixty-four hours. In the meantime, urine was passing unobstructed through the ureters and could be seen spurting from the ureteral orifices. An intravenous urogram showed no evidence of obstruction on either side, and the solution passed into the rectum unobstructed, after the channel had been established.

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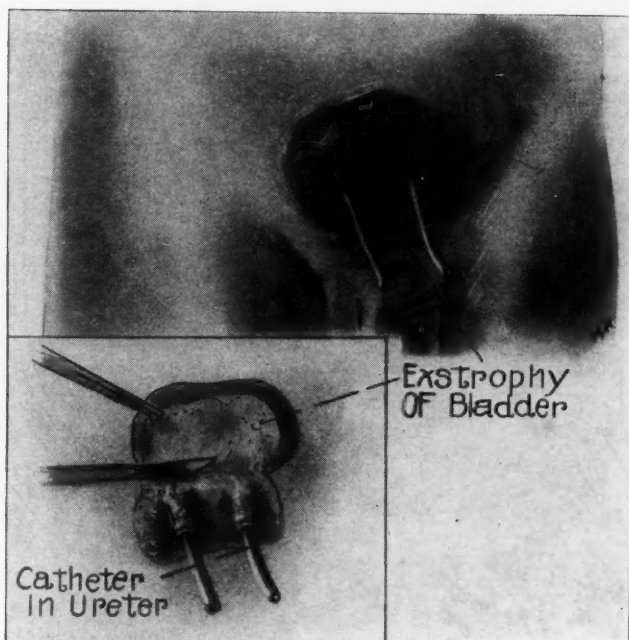


FIGURE 7.—Drawing showing (a) exstrophy of the bladder. Catheters *in situ*; (b) dissection of exstrophic bladder. The ureters are followed down and ligated as they emerge from the trough in the bowel.

### Second operation:

The second operation was performed ten days later. This included cystectomy and severance of the continuity of the ureters with removal of the lower segments of the ureters (Figs. 8 and 9). The exstrophic bladder was removed by the usual technique. The two ureters were easily followed down to the point where they emerged from the trough in the bowel and there were divided and ligated. The skin about the periphery of the defect in the abdominal wall was undermined and the skin edges were reapproximated with silk sutures, and with stay sutures of silkworm gut. The child's condition was satisfactory at the completion of the operation.

Eight days after operation, the child was discharged from the hospital. At that time, the intravenous urogram showed normal findings (Fig. 10). The total period of hospitalization was twenty-one days. One year later, a letter from the patient's physician stated that the child was in excellent physical condition.

### CONCLUSIONS

Transplantation of the ureters for exstrophy of the bladder should be performed as soon as there is positive evidence that the rectal sphincter is functioning adequately. The earlier the operation, the

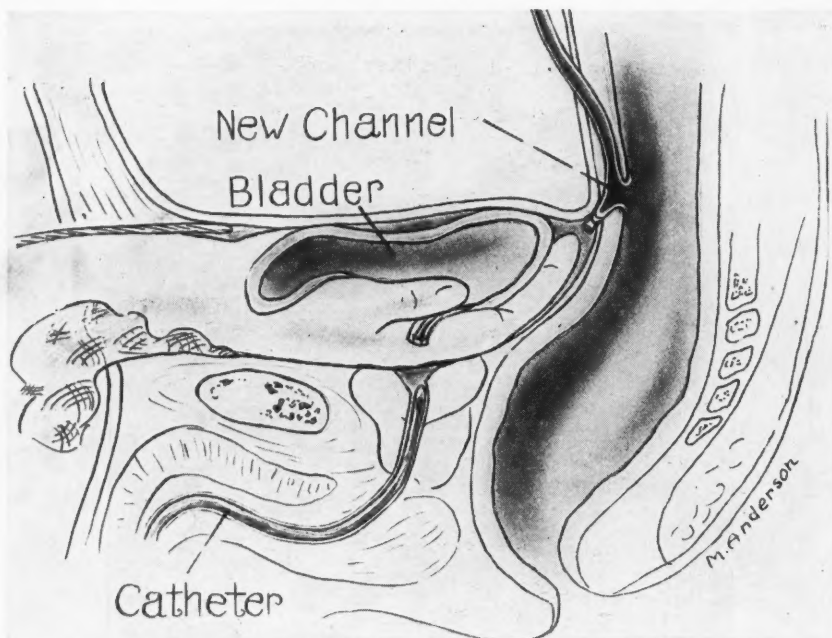


FIGURE 8.—Drawing showing the final stage of cystectomy starting at the bladder neck.

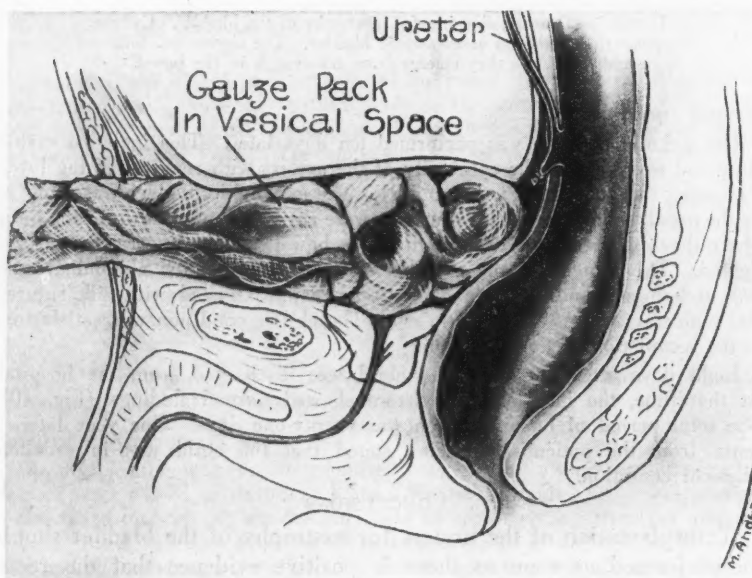


FIGURE 9.—Drawing showing the cystectomy completed. The vesical space is packed with gauze.



## URETERAL TRANSPLANTATION

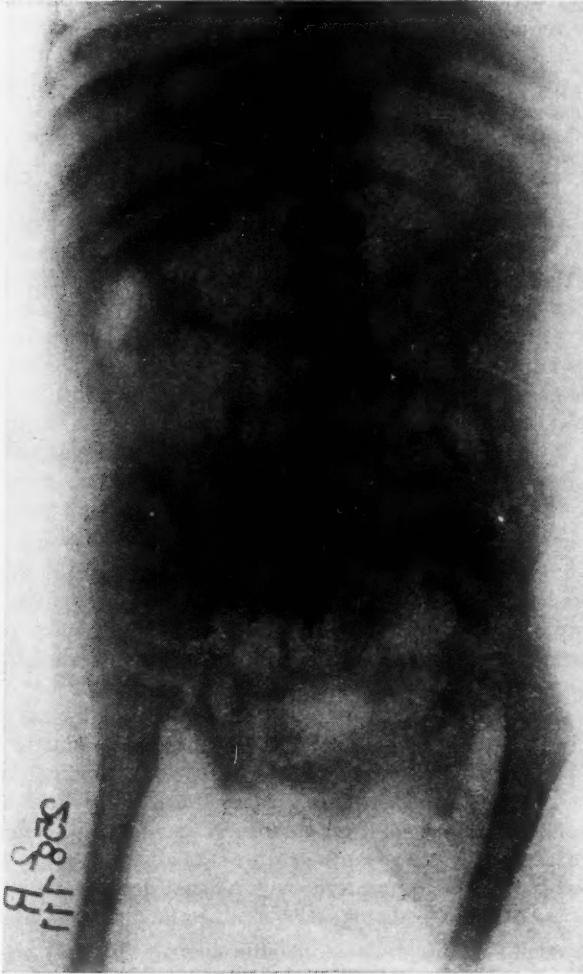


FIGURE 10.—Postoperative urogram shows no evidence of stasis. There is no evidence of the dye in the kidneys at the end of one hour.

better the chance for avoiding the development of hydronephrosis and hydro-ureter with the renal infection and functional impairment which frequently are seen in older children in whom the operation has been delayed.

A technique is described by which both ureters may be transplanted simultaneously. This procedure is accompanied by only slight post-

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operative reaction and the time required for hospitalization is materially reduced.

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## DEFICIENCY DISEASE IN ELDERLY PEOPLE

JOHN TUCKER, M.D.

Various nutritional disturbances occur quite commonly during all periods of life. However, they are more likely to produce distressing symptoms in infancy and in old age. In infancy and childhood, the anabolic processes impose great demands for the growth of tissue, and the well-balanced diet must include adequate quantities of proteins, fats, carbohydrates, minerals and vitamins. When a proper quantity of these substances is lacking, we are confronted, sooner or later, with various disturbances in growth and nutrition which are classified as deficiency disease. However, the modern training of pediatricians, the activities of various health agencies and of the Press have served to sensitize and educate mothers concerning proper foods for their children. These efforts have lowered infant mortality and resulted in a greater proportion of more sturdy youngsters. The addition of proper vitamins has served also to compensate to a great degree for the ultra refinement or concentration of certain foods and to assure healthy growth during the dark winter months.

Among the elderly members of the household, however, the situation may be quite different. There is no organized effort on the part of the family or society to supervise their dietary habits. Very commonly, old people eat excessive quantities of carbohydrates which supply more calories than are warranted by their physical activities. Then, too, the foods selected very often are deficient in iron and in vitamin B, and they may lack many important and indispensable amino acids. As the result of such deficiencies in iron, protein and essential vitamins—particularly vitamin B—the bone marrow receives an inadequate supply of materials which are necessary to build and mature blood cells. Anabolism and catabolism are present at all ages, and the latter is more and more predominant as senility approaches. Therefore, proper materials must be supplied for the rebuilding of destroyed body cells, and the fluid environment of these cells must be satisfactory.

We know very little concerning the factors which influence the degenerative changes in old age. In the vast majority of patients we find that the degeneration is in the cardio-vascular renal system. Often there are disturbances in one organ or another due to a narrowing or obliteration of capillaries. Also, we realize that infectious diseases such as rheumatic fever, scarlet fever and syphilis have a certain predilection for blood vessels, and may hasten degenerative changes. However, as life progresses and the wear and tear of living increases, the individual will endanger his health and longevity if he fails to eat, absorb or assimilate the building stones which are required to repair or replace damaged cells.

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Each year we see an increasing number of patients who are beyond middle life and who, as a rule, have symptoms due to degenerative diseases. In addition to this, we find many among them who show unmistakable evidence of deficiency disease. The association of these two conditions may produce an exaggeration of the symptoms of degenerative disease so that the very common complaints are fatigue, dyspnea, dizziness or failing memory, and in such cases, a thorough examination and a correct diagnosis are essential even though the patient may be beyond the sixth decade of life. If a typical picture is presented of pellagra, sprue, or pernicious anemia, the diagnosis can usually be made without great effort or expense. In the border line cases, however, proper laboratory and clinical facilities must be employed. If our experience and our interest in the problem are adequate, we are able to collect evidence from the clinical and laboratory sources, which will lead us to the correct diagnosis.

To illustrate, let us assume that we are dealing with an elderly patient who has fairly advanced arteriosclerosis. For many years, the diet has been faulty, and for a long time, he has obtained poor meat, his vegetables have been low in iron content, and he has failed to eat adequate amounts of the foods which are rich in vitamins. As a result, a fairly severe grade of anemia has developed. Unless this patient's heart is able to increase its load and maintain an increased minute volume of blood through the capillaries, or if the capillaries are unable to dilate to the required degree, the patient will suffer from tissue anoxemia. This may occur in the brain, the joints, the kidneys, or elsewhere in the body. Among our cases of pernicious anemia in elderly people—and pernicious anemia is well recognized as a deficiency disease—our therapeutic results show that an exaggerated state of tissue anoxemia often is present. By careful study, we usually can determine whether the anoxemia is the result of a faulty diet, excessive elimination of essential food elements such as occurs in the presence of chronic diarrhea, or whether it is the result of disturbed digestion of food or of deficient absorption of food from the intestinal tract. This necessitates a careful examination of the blood which includes an accurate estimation of the hemoglobin, determination of the color index, volume and saturation index and icterus index. When we add these findings to the clinical features such as glossitis or an atrophic tongue, gastric achlorhydria, and neurological changes, a diagnosis of iron-deficiency anemia, or of pernicious anemia may be made. Obviously, other types of anemia such as the anemia of pregnancy, of hemorrhage, of nephritis, of chemical poisoning and of tapeworm infestation necessarily must be considered. In any case, however, the symptoms of degenerative disease will be increased or modified by the degree of anemia which is present. Should we fail to make a complete diagnosis

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in such a case, we could scarcely expect to prescribe the proper treatment which would lead to satisfactory therapeutic results.

In an effort to obtain further information on this subject, we made a careful survey of the clinical records of 50 patients with pernicious anemia whose ages were in the sixth, seventh and eighth decades of life. In each case, the diagnosis of pernicious anemia was based upon a characteristic macrocytosis of the red cells, a color index above one, an absence of free hydrochloric acid in the stomach as determined by the Ewald test meal, and frequently glossitis or atrophy of the tongue, and in many instances, the clinical picture of subacute degeneration of the spinal cord. In all but two patients, definite associated conditions, such as arteriosclerosis, diabetes, cardiac insufficiency and various abnormalities in the gastro-intestinal system were found which contributed to the symptomatology. So far as we could determine, the diagnosis of pernicious anemia had not been made prior to an examination in 44 (88 per cent) of the cases which were studied, but the symptoms had been attributed to other pathological states. A correct diagnosis had been made elsewhere in 16 instances (32 per cent) and of these, only six patients had taken a sufficient quantity of liver to maintain the red cell level at 4 million per cm. As a result, all but two of the patients had one or more of the following symptoms: weakness, shortness of breath, failing memory, failing vision, sore tongue and various degrees of numbness and ataxia. While these symptoms can occur in patients with degenerative diseases who have no clinical anemia, our study has convinced us that in this series of cases, pernicious anemia played an important and often the major rôle in the symptomatology.

The following three cases illustrated some of the diagnostic problems which we have encountered and the treatment which has been used.

*Case 1:* A woman, 73 years of age, came to the Clinic complaining of extreme fatigue, pains in the joints, numbness in the fingers and slight soreness of the tongue. The admission diagnosis was arteriosclerosis and hypertrophic osteoarthritis. Physical examination showed these two diseases were present in a quite marked degree. It was found that the patient had a moderate degree of glossitis, a gastric free acidity of 0 and considerable pallor which led us to suspect the presence of pernicious anemia. Examination of the blood revealed 1,990,000 red blood cells, hemoglobin, 55 per cent (Haden-Hausser); volume index, 1.4; saturation index, 0.98; and icterus index, 20.

*Treatment:* Liver extract was administered in doses of 3 cc. intramuscularly daily for two weeks. A high vitamin diet and one-half pound of cooked liver three times a week was prescribed. As soon as the blood count reached normal, a maintenance dose of 3 cc. of liver extract intramuscularly once a week and the same diet of liver was used. As soon as the blood returned to normal, the joint pains disappeared and other symptoms were alleviated with the exception of

## JOHN TUCKER

numbness in the fingers. When the patient was seen last, 22 months after treatment was begun, her physical strength and mental vigor were normal.

*Comment:* This patient, who had symptoms which appeared to be due to arteriosclerosis and hypertrophic osteoarthritis, was restored to satisfactory health by the adequate treatment of pernicious anemia.

*Case 2:* The patient, a woman 62 years of age, complained of intermittent attacks of nausea and vomiting which had been present for ten years. A previous examination in another city showed an obstructing lesion at the outlet of the stomach and a diagnosis of carcinoma of the pylorus had been made. The principal symptoms were nausea and vomiting, weakness, shortness of breath and a weight loss of 10 pounds in 6 months.

Roentgen examination of the stomach showed that the deformity was due to a diverticulum of the second part of the duodenum which exerted pressure on the duodenal bulb and pyloric antrum. It was evident that the mechanical obstruction was the cause of the vomiting. The Ewald test meal was negative for free hydrochloric acid. The tongue was red and sore, and the neurological examination revealed sensory and reflex abnormalities in the lower extremities which were characteristic of combined degeneration of the spinal cord. Examination of the blood revealed a severe grade of pernicious anemia. The blood examination showed 2,260,000 red blood cells; hemoglobin, 55 per cent; color index, 1.22; volume index, 1.33; saturation index, 0.92; icterus index, 4.0.

*Treatment:* Anti-anemic treatment consisted of daily intramuscular injections of 3 cc. of liver extract for 17 days, one teaspoonful of dilute hydrochloric acid by mouth with each meal, Haliver oil capsules three times a day, and a pernicious anemia diet. Following this parenteral liver therapy, 1 ounce of liver extract by mouth four times a day was used, and the hydrochloric acid was continued. This was gradually reduced to 1 ounce of liver extract daily. The reticulocyte response to intramuscular liver therapy was 9.7 per cent in eight days. In seven weeks, the blood examination showed red blood cells, 4,580,000; hemoglobin, 84 per cent; color index, 0.91; volume index, 1.09; saturation index, 0.84; icterus index, 3.0. The clinical improvement, likewise, was prompt and striking. Vomiting ceased, the strength and weight returned to normal, and the glossitis and the ataxia or tingling in the lower extremities cleared up.

*Comment:* It appears that two therapeutic procedures were responsible for the satisfactory results in this case. First, the period of bed rest was undoubtedly responsible for the relief of the pyloric obstruction, and second, the specific anti-anemia treatment cleared up the deficiency symptoms. The patient has remained in excellent health for two years and as yet, no surgical interference has been necessary.

*Case 3:* The patient was a woman 64 years of age who was admitted to the hospital with the diagnosis of chronic nephritis. She had been troubled with swelling of the feet and ankles for 4 or 5 years which was accompanied by palpitation and dyspnea, swelling of the eyelids and numbness of the hands and feet. The tongue was atrophic, the gastric contents showed no free hydrochloric acid, and there was some dehydration. The skin was dry, and it was pale and yellowish in color. The spleen and liver were palpable. The sensorium was quite clouded. The urea clearance test showed 48 per cent function at the end of the first hour and 56 per cent at the end of the second hour.



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The serum protein was 5.86—albumin 3.63, globulin, 2.23. Examination of the blood showed 1,030,000 red blood cells; hemoglobin, 32 per cent; color index, 1.52; volume index, 1.66; saturation index, 0.91; icterus index, 10.0. Specific liver therapy for pernicious anemia was administered, and in three and one-half months, examination of the blood revealed 5,180,000 red blood cells; hemoglobin, 84 per cent; color index, 0.81; volume index, 0.91; saturation index, 0.89; icterus index, 4. The maximum reticulocyte response was 31.6 per cent on the sixth day of treatment.

The therapeutic results were most satisfactory. When the anemia was alleviated, the edema, air hunger, fatigue, mental confusion, and the dryness of the skin had entirely disappeared and only a slight residual numbness in the feet remained.

*Comment:* The satisfactory results in this case are sufficient evidence to show that the anemia was not due to chronic nephritis but to a deficiency of the specific anti-anemia substances which are present in liver and liver extract.

In elderly patients who may have one or more forms of degenerative disease, one can very easily overlook cases of atypical pernicious anemia. Unless complete blood studies are made in a well-equipped blood laboratory, a proper classification of the anemia cannot be made. We do not believe that pernicious anemia is especially common in elderly people; however, when it does occur and when the diagnosis is made, the result of treatment is fully as satisfactory as it is in younger people provided degeneration of the body has not progressed too far.

## RECURRENT DISLOCATION OF THE PATELLA

JAMES A. DICKSON, M.D.

The subject of slipping or dislocated patella is one regarding which much has been written and it has been discussed on so many occasions that one almost feels that an apology should be offered for an attempt to add anything to what has been said already regarding this condition. However, there are still several controversial points, and it is felt that our personal experience may prove of interest.

Slipping patella is the result of an abnormal laxity of the supporting structures about the knee which permits the occasional displacement of the patella to the outer side of the external condyle of the femur. The underlying predisposing causes may be (1) acquired or traumatic, (2) structural or congenital. The true congenital dislocations are those in which the patella develops away from its normal position and are not considered in this communication.

Trauma may be the original cause of a dislocation of the patella. In such cases, following a severe injury which is accompanied by a rupture of the quadriceps muscle, expansion on the inner aspect of the patella causes the knee to remain insecure, especially on extension against resistance, as for example, in descending stairs. But by far the greater number of dislocations of the patella occur without any such injury and are associated with predisposing structural conditions. The first and most important of these is a genu valgum deformity in which the pull of the quadriceps tends to displace the patella outward. Other such structural conditions may be an underdevelopment of the lateral condyle of the femur, abnormal lateral displacement of the tibial tubercle, relaxation of the capsular ligaments on the inner side of the knee, or of other patellar attachments. The relaxed patellar tendon is a very important predisposing factor in the production of dislocation of the patella. The cases which follow infantile paralysis fall into this group.

Conservative treatment with braces and supports has given temporary relief but has never been successful in effecting a cure.

Many types of operation have been suggested, such as those of Goldthwait, Krogius, Gallie, Soutter, Wagner and Albee. Some of these operations are directed toward the tightening and reinforcement of the relaxed structures on the medial side of the patella. In others, the attempt is made to straighten the direction of the pull of the extensor mechanism, while in Albee's operation the lateral condyle of the femur is raised.

The operation that I have found very satisfactory is based on the principles laid down by the above authors except that I have not found

## RECURRENT DISLOCATION OF THE PATELLA

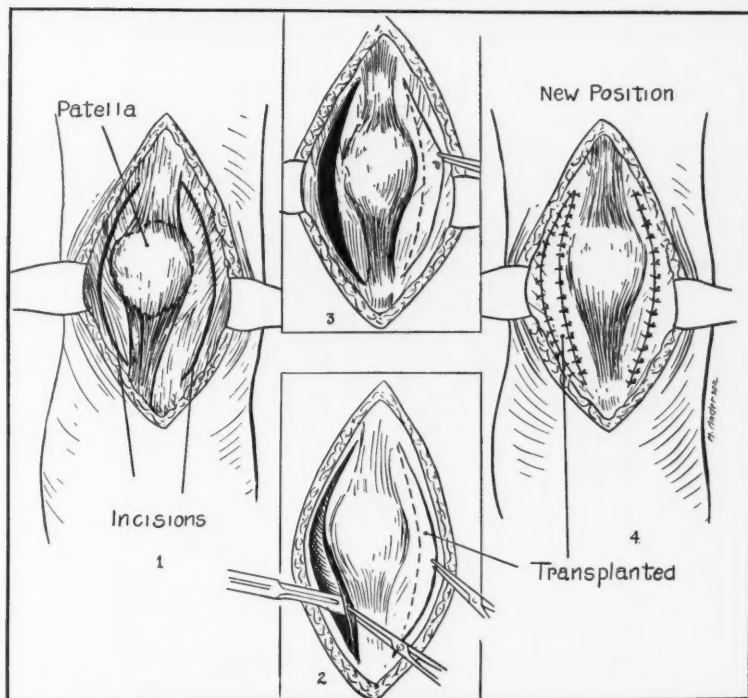


FIGURE 1:1.—Exposure of patella showing the usual lateral attachment of the patellar tendon and the position of incisions in the capsule.

FIGURE 1:2.—Lateral incisions through capsule and freeing of patellar tendon sufficiently to allow proper medial displacement.

FIGURE 1:3.—Extensor apparatus brought into a straight line in order to determine the necessary amount of internal capsule to be excised.

FIGURE 1:4.—Extensor apparatus in proper position and transplanted portion of capsule in place.

it necessary to resort to the Albee operation. The operative treatment is aimed to bring about a condition that will allow the extensor apparatus to pull in a straight line and at the same time will correct the relaxation of the medial capsular ligament.

A tourniquet is applied, a slightly curved incision is made to the inner side of the patellar tendon and the skin and subcutaneous tissues are retracted. The capsule then is divided on both sides of the patella without disturbing the synovial membrane (Fig. 1:1). The patellar tendon is divided with its periosteal attachments and the periosteum is stripped up from the tibia (Fig. 1:2). The patella then is moved inward and the lateral incisions prolonged upward until the extensor apparatus is pulling in a straight line. The patellar tendon is given a

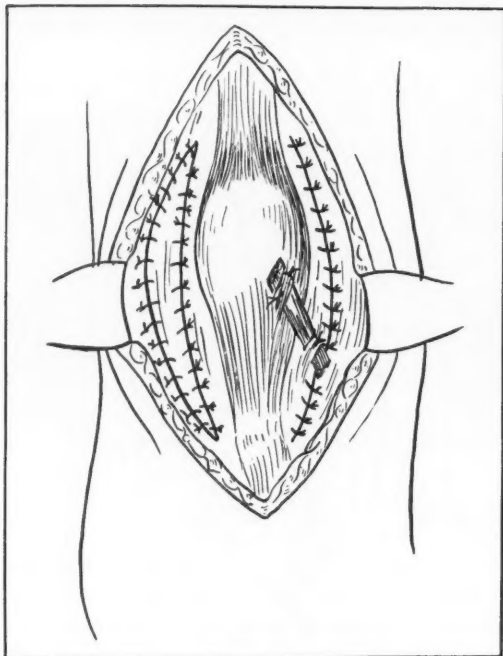


FIGURE 2.—Completed operation when strip of fascia lata is used to reinforce internal lateral ligament.

new attachment medially and is firmly sutured to the periosteum in this position. Enough of the redundant portion of the internal capsule then is excised to hold the patella in its proper position (Fig. 1:3). The excised portion of the capsule is transplanted and used to fill in the defect on the outer side of the joint (Fig. 1:4).

After this stage of the operation is completed, it has been felt advisable in some cases to add a fascial band to support the internal lateral ligament, along the lines advocated by Gallie and by Soutter (Fig. 2). Each of these modifications has been used with satisfactory results. I have not used these operations alone because I felt that it was of paramount importance to correct the mechanical pull of the patellar tendon before all else. When the operation is completed, the tourniquet is removed, and the skin is closed in the usual manner. A plaster of paris cast is applied for a period of three weeks, after which physiotherapy and exercises for the quadriceps are started. The patient is encouraged to walk in about six weeks.

The capsuloplasty operation which I have described has been performed in ten cases. In two cases, the internal lateral ligament was

### RECURRENT DISLOCATION OF THE PATELLA

reinforced with fascia according to the Gallie procedure and in one according to the Soutter method. In two cases of severe knock-knee, the deformity was corrected by osteotomy before the capsuloplasty was done.

The results in all cases have been exceedingly gratifying and there have been no recurrences of the dislocation. It is possible in some of the cases that one of the less radical operations might have proved effective. However, as failures and recurrences are reported by those who have employed the various methods cited above, I feel that the more painstaking operation is warranted.

## THE MANAGEMENT OF FUNCTIONAL MENSTRUAL DISORDERS

E. PERRY McCULLAGH, M.D.

The majority of menstrual disorders are due to some derangement in the function of the ovaries. This may be due to factors which influence the general health or to more specific factors which alter the production of the hormones of the ovaries in one of several ways, i.e., (a) by affecting them directly, (b) by affecting their chief governing agent, the pituitary gland, or (c) through other endocrine glands, notably the thyroid or adrenal glands. In this paper, we shall deal with treatment of menstrual disorders chiefly from an endocrine point of view. The physiology of menstruation will be summarized briefly. We shall then examine the available hormonal and nonhormonal remedies, and discuss the application of these agents to menstrual disorders of known or presumed endocrine origin and to some of uncertain etiology.

### PHYSIOLOGY

Sex is determined primarily by the gene, but the development of the sexual apparatus is dependent to a large degree upon the hormones elaborated by the sex cells. No new structures are formed in the body by the action of hormones, maleness and femaleness depending upon the degree of differentiation of structures already laid down. Male sex hormone acting prior to the time of sex differentiation causes development of sex organs of male character while female sex hormone (estrin) acting before the time of differentiation causes these structures to assume the female characteristics and is necessary for the maintenance of normal structure and function.

Estrin is elaborated chiefly by the graafian follicles and exists in several forms. Which of these forms is most important in normal body economy is not known. Estrus is a cyclic heightening of sexual excitement commonly known as "heat" or "rut" which has been studied in rodents and has formed the basis for most of our knowledge of the physiology of estrin. The estrous cycle has been divided into several parts. In dioestrus or the resting phase the ovaries are quiescent, the uterus is lined with low columnar epithelium, the vagina is lined by a thin layer of flat epithelial cells, and the vaginal smear contains many leucocytes. In proestrus, the follicle is seen to grow, the endometrium becomes deeper, and the vaginal mucosa becomes stratified. In full estrus, the follicle has reached the height of its growth, and it ruptures, freeing



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the ovum. The endometrium has become deeper and the glands larger, but they retain a simple test-tube-like structure; the cornified cells of the vaginal mucosa are cast off, and the vaginal smear shows only large, clear, non-nucleated cells. In the rodent, no corpus luteum is formed in the absence of pregnancy, and the changes described above regress through metestrus to dioestrus.

Thus far, the changes which occur in the rat and mouse are comparable to the changes which take place in the human from the beginning of the growth of the follicle at the time of the menses up to the time of the bursting of the follicle at the mid-menstrual period. In rodents, the occurrence of pregnancy is the signal for the formation and maintenance of a corpus luteum, whereas in the human, the corpus normally occurs and is maintained for a time after ovulation. Those changes which are present in the genital tract of the rodent after fertilization of the ovum occur as the result of a hormone known as progesterone which arises from the corpus luteum. It causes a great thickening of the endometrium, the surface of which is thrown into deep folds in preparation for the nidation of the fertilized ovum. The glands of the endometrium become tortuous, dip deeply into the uterine structure, and take on the appearance of actively secreting glands. This is the progestational endometrium and is comparable to the type which normally forms in the human during the latter half of the menstrual cycle.

The growth of the graafian follicle and the production of estrin is dependent upon the elaboration of an anterior pituitary hormone commonly called prolactin-A, and according to current belief, the occurrence of a corpus luteum with its production of progesterone depends upon the elaboration of a second sex hormone from the anterior lobe of the pituitary which is known as prolactin-B.

The explanation of menstrual bleeding is less satisfactory. The following is the most commonly accepted theory at the present time: It is known that estrin in the human arises from both follicle and corpus luteum. It is generally accepted that estrin exerts a depressing effect upon the production of sex hormones by the pituitary gland. Therefore, after the follicle and the corpus luteum have produced a relatively large amount of estrin, the activity of the pituitary is said to become depressed, which in turn causes a disappearance of the corpus luteum, a loss of its power of maintenance of the endometrium with consequent sloughing and hemorrhage. Such an explanation is not entirely satisfactory for several reasons, one of which is that blood may be seen

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prior to menstruation among the endometrial interstices without obvious associated evidence of endometrial disintegration. Also, the experiments of Werner and Collier<sup>1</sup> appear to indicate that cyclic menstrual bleeding may occur in castrated women who are treated with estrin alone. During pregnancy, maintenance of the corpus luteum results in growth of the endometrium and formation of the decidua. Other ovarian hormones probably exist but they will not be discussed here.

When the above knowledge of the physiology of menstruation is applied, we see that a marked underproduction of ovarian sex hormones before puberty results in profound underdevelopment of uterus, tubes, vagina, secondary sex glands, secondary sex characteristics, and amenorrhea. A mild prepuberal hypo-pituitarism and hypo-ovarianism could cause development of the follicle without its proper maturation and thus a lack of corpora lutea. This in turn would cause underproduction of progestin, lack of maturation and improper overgrowth of the endometrium, with consequent amenorrhea, irregular menses or in the case of sloughing, functional menorrhagia. In early pregnancy, a lack of prolan-B is considered in some instances to be responsible for the improper maintenance of the decidua which results in bleeding or abortion.

Underproduction of estrin which occurs after the menses have been established may result in hypomenorrhea or amenorrhea together with a tendency to atrophy of those parts which are dependent on estrin for their maintenance, the degree of atrophy depending upon the degree of reduction in the supply of the substance. Other associated metabolic changes also take place. Prepuberal hyperovarianism results in too early menarche and development of sexual characteristics and may be associated clinically with evidence of masculinization and those signs which at times accompany adrenal tumors.

Hyperfunction of the pituitary gland may lead to overstimulation of the ovaries and the so-called hyperhormonal amenorrhea. Clinically, one sees many complex multi-glandular pictures which are related to this condition. Overproduction of prolan may be the result of a compensatory mechanism caused by ovarian hypofunction such as that which follows surgical castration or the menopause.

## AVAILABLE THERAPEUTIC AGENTS

### *A. Hormones*

*Pituitary Hormones:* No discussion of the proposed differences between gonad-stimulating hormones of pregnancy urine and those from the pituitary is necessary here. Some pregnancy urine extracts which are in common clinical use are antuitrin-S (Parke-Davis), Fol-

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lutein (Squibb), and A. P. L. (Ayerst, McKenna & Harrison). Regardless of the physiology which is involved, it should be borne in mind that from a clinical standpoint these substances generally are more effective in reducing the menstrual flow than in increasing it.

Pituitary sex hormone which is made from horse pituitaries is now available under the name of prephysin (Chappel Bros.) and it is standardized to have proportionately more follicle-stimulating than luteinizing effect. It is for this reason that it has been proposed for the treatment of sterility.

Pituitrin or other posterior lobe extracts are occasionally useful in the management of acute menorrhagia.

*Ovarian Hormones:* Urine from pregnant women also is the chief source of supply of estrin for therapeutic use, although Amniotin (Squibb) is made from amniotic fluid and Emmenin (Ayerst, McKenna & Harrison) is made from placenta. Popular forms of estrin for hypodermic use are Theelin-in-oil (1,000 and 2,000 international units in 1 cc. ampules) (Parke-Davis), Amniotin (Squibb) in 500 units in 10 cc. vials, Progynon (Schering) in 1 cc. ampules, 125 international units per cc., and Progynon-B (Schering) in ampules of 2,500, 10,000, and 50,000 units' strength, Folliculin-Menformon available through H. H. Beissner & Co., New York (1,000 units per cc.).

Theelol (Parke-Davis), Amniotin, Progynon, Emmenin and Menformon are available for oral administration.

*Thyroid Hormones:* Desiccated thyroid or whole gland (the latter one-fifth the strength of the former) is still a very useful adjunct in the hormonal management of menstrual disorders. This is used alone or in addition to other forms of therapy. Small doses are usually quite as effective as large ones, except where the indications for thyroid are especially clear cut.

*Insulin:* According to recent reports, insulin occasionally may be a useful adjunct. I have observed a few cases of amenorrhea where sex hormone therapy has failed to produce clinical results alone but a good clinical response has been obtained following a short course of adrenal cortical hormone in the form of eschatin (Parke-Davis). The use of insulin and eschatin, however, must be very limited and at present is entirely empirical.

*Progestin* is not, so far as I am aware, available in a well standardized form for clinical use.

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*B. Non-Hormonal Agents*

The general physical condition of the patient is of great importance. Menstrual disorders occasionally correct themselves after the weight of an obese patient has been reduced or after weight has been gained by a malnourished woman. The therapeutic value of exercise, fresh air and sunshine must not be overlooked. More specific nutritional factors, such as a relative deficiency in vitamins, especially in B and E, may need correction, as it is known that these substances influence the activity of the pituitary and ovary considerably. Vitamin B is easily supplied if the diet contains sufficient dark cereals, or yeast or yeast concentrates may be used. Fresh vegetables or wheat germ are excellent sources of vitamin E. That fright or anxiety may cause irregular menses or amenorrhea is common knowledge, and the psychic factor must be taken into consideration.

If anemia is present, the use of iron may be required. Simple microcytic anemia with or without achlorhydria will usually respond well to iron if it is administered in sufficiently large doses, sometimes 60 or even as high as 120 grains per day of Bland's mass may be necessary. Liver or stomach therapy may be useful.

Infection in the pelvis requires treatment according to the indications of each individual case. Tuberculosis, syphilis or other general infections may require special care. Undulant fever causes amenorrhea not infrequently, and it sometimes is associated with signs of encephalitis, which usually is of a mild grade.

Radiation therapy is very useful in some cases. Sometimes from 10 to 25 per cent of an erythema dose to the pituitary will cure amenorrhea when other measures have failed to do so and even 60 or 70 per cent of an erythema dose to this gland appears to be entirely harmless. I still hesitate, however, to apply x-ray to the ovaries even in the so-called stimulating dosage unless all other measures have been given an adequate trial and have failed.

In my opinion, the application of radium to the uterine canal in small doses, from 800 to 1,400 milligram hours, is the treatment of choice where general measures have failed to control functional menorrhagia. By the use of this method, we avoid the outspoken castration effects which are produced by heavy doses of x-ray therapy and also avoid the constant risk which attends hysterectomy. In malignancy of the fundus uteri, hysterectomy undoubtedly is the treatment of choice.

DIAGNOSIS AND TREATMENT

In this discussion of the diagnosis of menstrual disorders, the matter will be examined chiefly from the point of view of etiology. I believe the fact that our diagnostic acumen in this field is inadequate, makes it

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doubly important that we use all available means for making a correct diagnosis.

Many attempt to deduce what sort of ovarian dysfunction is present from an evaluation of the amount and character of the menstrual flow alone, and usually, a pelvic examination in itself yields no positive information. In all cases, therefore a painstaking history should be taken, a careful general examination and examination of the urine and blood should be made, and usually the basal metabolic rate should be estimated. The possible presence of a pituitary tumor should always be remembered, and roentgenograms of the skull should be made and visual field examination done when these examinations are indicated. When bio-assays for sex hormones are available, they often are very useful adjuncts.

### THE PITUITARY AND FUNCTIONAL MENORRHAGIA

Physical examination usually yields no evidence of hypofunction of the pituitary when it is of the mild prepuberal type which is the presumed cause of functional menorrhagia. It has been my practice that young girls and women under 30 years of age whose pelves are normal should not be subjected to curettement of the uterus. Beyond this age, diagnostic curettage must be advised, if we are to avoid treating medically some cases of carcinoma of the fundus. If no evidence of neoplasm is evident and especially where endometrial hyperplasia is found, large doses of prolan should be administered. In general, in those cases in which less than the normal amount of endometrium is found, the response to such therapy is poor. Among such cases are examples of so-called anovular bleeding. More consistent results are to be expected near the menarche than near the menopause, although it is a remarkable fact that menorrhagia occurring at the menopause will in many instances respond well to such therapy, and this is true in spite of the fact that prolan assays usually show that the urine already contains a measurable excess of the substance.

Our personal experience with prolan therapy is limited almost entirely to antuitrin-S which has been used for this purpose for several years. The dose usually employed is from 1 to 2 cc. (100 to 200 units) daily for a period of from one to three months, but this period may be shortened if results are obtained earlier. If good results are not obtained in three months, further treatment will be useless in most cases. Occasionally, larger doses may be given at times when the bleeding is more severe. In rare instances, single doses as high as 5 cc. have been used without apparent harm. Severe hemorrhage may require other measures and for this purpose, ergot by mouth or by hypodermic may be efficacious as an emergency measure. Rest in bed and application

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of cold to the lower abdomen may be useful. Curettage and packing may be required and sometimes in the beginning, massive doses of estrin alone or together with pituitrin will produce rapid effects, although of course, the continued use of estrin therapy is contraindicated under such circumstances. The results of prolan therapy in functional menorrhagia are generally excellent, and we have obtained satisfactory clinical results in over 80 per cent of selected cases. Usually, only one course of treatment is necessary, but it may be necessary to repeat the course in some cases.

The use of radium has been mentioned above.

*Hypopituitarism:* In more severe prepuberal pituitary failure, general evidences of disease of this gland may be present. One must keep in mind pituitary dwarfism of the microsomatic or Lorain-Levi type and Fröhlich's syndrome which are extreme disorders of this type, the latter probably being associated with hypothalamic damage. Pituitary failure may be evidenced not only by mild or definite dwarfism but by other signs, such as tapering of the fingers, spacing of the teeth, and unusually fine texture, dryness or hairlessness of the skin. Obesity of the cerebral type, polydipsia, polyuria, polyphagia, or somnolence may suggest hypothalamic damage. Evidences of hypogonadism may be present, such as late menarche, relative underdevelopment of the genitalia and secondary sex characteristics. Amenorrhea frequently is a symptom, as are hypomenorrhea and oligomenorrhea. In such instances, the presence of a pituitary tumor should be carefully ruled out, and the glucose tolerance may be altered sufficiently to be of diagnostic significance. A low basal metabolic rate and habitually low or absent urinary prolan are consistent with a diagnosis of pituitary disease. In such cases, assays almost invariably show a diminished amount of estrin.

In cases where a pituitary tumor is present, it should be treated by x-ray or surgery. The general health and disturbances in weight should be corrected, and if reducing diets are necessary, great care should be exercised that vitamin deficiencies or anemia are not produced.

In the treatment of hypopituitarism, prolan or prephysin may be used in small amounts such as one-half cc. three times weekly in addition to theelin or estrin in some other form. Estrin may be given in doses of 1,000 or 2,000 units daily hypodermically or in larger doses by mouth. Some workers are using progynon-B in doses as large as 10,000 units every third or fourth day for three weeks and Proluton (Schering) for a few doses during the fourth week. From one-half to two grains per day of thyroid (desiccated) are often prescribed as well.

The results of such treatment are not particularly encouraging. In the more severe cases, if menstrual bleeding occurs at all, it is usually not normal and may disappear entirely when the treatment is discon-



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tinued. In the milder cases, good results often are obtained, and the menses may remain normal after cessation of these measures. I have seen cases of unquestionable pituitary disease in which measures similar to those mentioned above have been followed by reestablishment of the menses after five and eight years of amenorrhea respectively, but such results are not the rule. In not a few instances, there may be sufficient improvement in the general health and sense of well being to warrant the partial continuation of these measures, even though menstruation may not be resumed normally.

*Hyperfunction of the pituitary gland:* So far as the growth hormone is concerned, hyperfunction of the pituitary gland is not a common finding in the early life in women, gigantism usually occurring in men. Hyperpituitarism of the type accompanying the so-called polyglandular disease or pituitary adrenal syndrome (Cushing's syndrome—pituitary basophilism) occurs in a mild form quite frequently. It is difficult, if not impossible, to differentiate this from the adreno-genital syndrome clinically. In outspoken cases, obesity is present which is confined chiefly to the trunk, head, and neck, and hirsutism, amenorrhea, purple striae atrophica, large breasts, polycythemia, mental dullness, excitability, tremor, tachycardia and sometimes elevated blood pressure and elevated basal metabolic rate are found also. In such cases, the Friedmann test frequently gives positive findings and peculiarly enough, there are no clinical evidences of hypo-ovarianism to be found except that there is amenorrhea; in spite of the high urinary prolan, urinary estrin usually is very low.

Mild cases of this sort are frequently encountered in young women who complain of scanty or irregular menses or amenorrhea. The patient is usually a healthy, robust type, alert and active. As a rule, the body is broad and thick, the breasts rather large, and there is a tendency to obesity. A distinct trend toward male deportment is often obvious. The polycythemia and purple striae are absent but mild hypertrichosis of the face and a tendency to male escutcheon of pubic hair are common. Positive Friedmann tests are commonly found and the urinary estrin is low. This type of patient may be benefited by estrin therapy but in my experience, this type represents the group which is most frequently helped by the administration of x-ray to the pituitary. From 10 to 25 per cent of an erythema dose may be all that is required, or the dose may be increased to 75 per cent or more in some cases if necessary. Severe cases will not respond well to roentgen therapy as a rule, but in many instances, the symptoms may be completely controlled by adrenal surgery which consists either of bilateral denervation or of partial adrenalectomy. The remarkable response after adrenal surgery which is seen in some such cases makes it quite clear that many of the symptoms are due to disturbances of the adrenal gland. Such improve-

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ment may occur even when the syndrome is associated with a proven tumor of the anterior lobe of the pituitary. It should not be forgotten that a similar clinical picture may be associated with a definite adrenal tumor or a masculinizing tumor of the ovary (arrhenoblastoma).

*Hyperpituitarism of a compensatory type* may follow hypo-ovarianism at any time during the menstrual life of a woman or at the natural menopause. The external evidences of the excessive production of sex hormones may be scant or absent. Recurrent headaches of migrainous or non-migrainous character which occur prior to or at the time of menses or near the menopause may be found to be associated in some instances, as Kurzrok<sup>2</sup> has shown, with an excessive amount of prolactin. Such headaches may at times be markedly benefited or eradicated by the use of estrin in relatively large doses—1,000 to 3,000 units per day. The control of such headaches may require a smaller dose throughout the month and an increase in dosage at or about the time when the headache is likely to occur.

#### OVARIES

*Prepuberal Hypo-ovarianism:* A marked degree of hypofunction of the ovaries which is of the prepuberal type and which is unaccompanied by any clinical evidence of pituitary disease is uncommon. When it occurs, one finds primary amenorrhea, infantile genitalia, absence of pubic and axillary hair, infantile breasts and nipples. The patient is usually tall and since the epiphyses of the long bones close late, the span may be several inches greater than the height. Sexual libido is slight or absent. In milder cases, there may be a delay in the menarche past the average normal time of 13½ years; the genitalia may be hypoplastic, the uterine canal measuring less than 7 cm. in length; the secondary sexual characteristics may be underdeveloped; and roentgenograms may show a distinct delay in epiphyseal closure. Such a slowing of epiphyseal growth occurs also in the hypothyroidism of childhood, in which case it almost invariably is associated with a distinct increase in the blood cholesterol. Large doses of estrin appear to be necessary in the treatment of most of these cases. We have used from 1,000 to 2,000 units per day for periods of many months. In addition to these measures, gonad-stimulating substances, such as antuitrin-S or prephysin in one-half or one cc. doses every second or third day may be used. If one attempts to increase the dose of estrin to a point where normal amounts of the substance can be obtained by assay from the urine, it will be found that doses as large as 10,000 units every second or third day may be necessary.

Here again in the severe cases, estrin therapy, even when large doses are used over long intervals, may yield only meagre results. Some growth of the vagina and uterus may be obtained and some increase in

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body hair and size of the breasts may occur. The menses, however, usually do not occur, and if they do, complete normality is rarely obtained and cessation of treatment usually will be followed again by amenorrhea. In the milder cases, the periods may become normally established or hypomenorrhea may be definitely benefited.

*Hypo-ovarianism of the late or secondary type* is very common, occurring in mild or severe form after pelvic inflammation, surgery, radiation therapy or in association with the natural menopause. The emotional and nervous changes, including the sympathetic nervous changes with hot flashes are the most outspoken symptoms. In mild cases, hypomenorrhea is common but it may not occur. Assays may show a constant deficiency in urinary estrin, and clinical signs such as mild genital atrophy, breast atrophy, general weight gain, together with trochanteric and large anterior malleolar fat pads may be present without any very obvious abnormality in the amount of the menstrual flow.

Estrin therapy is most efficacious and gives its greatest symptomatic benefit in cases of secondary hypo-ovarianism especially at the menopause. Here adequate dosage will apparently eradicate the symptoms in approximately 95 per cent of the cases. However, it is difficult to explain why even large doses fail to give symptomatic relief in some cases. It has been our practice to begin the treatment by prescribing 1,000 or 2,000 units of estrin by hypodermic in the form of menformon or Theelin-in-oil which is taken daily or every second day for from ten to twenty doses. This method not only gives prompt relief and increases the confidence of the patient in most instances, but also indicates as soon as possible those cases in which oral therapy will be worth a trial if symptoms recur, since if large hypodermic doses fail, certainly small doses by mouth will be valueless. In the cases where estrin therapy fails to correct the symptoms, hyperpituitarism can often be detected by prolan assay, and it is possible that x-ray therapy to the pituitary has not been utilized sufficiently under such circumstances.

The melancholia which occurs at the menopause may be relieved by treatment with large doses of estrin for long periods. The persistence of such therapy will, I believe, give complete recovery in many instances.

Prepuberal ovarian hyperfunction (*pubertas praecox*) is quite an uncommon condition, but it is obvious when it occurs. This condition is the complete antithesis of prepuberal hypogonadism and in its presence all the genital and secondary sexual changes are premature and there may be abnormally early epiphyseal closure with dwarfism. Such an abnormality may be associated with hyperadrenalism or adrenal tumor, and in severe cases, adrenal exploration, denervation or partial extirpation of the gland must be considered.

THYROID

*Prepuberal or childhood hypothyroidism* is a frequent cause of delayed menarche, or of irregular, scant or profuse menses. The diagnosis even in relatively severe cases is very frequently missed because in the mind of the physician, acquired hypothyroidism in children may not be clearly distinguished from cretinism. In childhood hypothyroidism, there is often nothing about the appearance of the patient to suggest the presence of the disease. Basal metabolic rate determinations are not dependable in childhood, although at the time of puberty or after puberty, they may be as useful as in the adult. The disorder should always be suspected where there has been abnormally slow growth, especially when late and irregular dentition has occurred. Coldness, lack of energy, edema, dry hair and nails and poor memory may be present. Roentgen evidence of delayed epiphyseal closure, together with a distinct hypercholesteremia are the most important diagnostic signs.

The treatment is obvious—thyroid is forced to tolerance, but it must be remembered that the symptoms of thyroid overdose are not identical in childhood and adult life. One-half grain of the desiccated thyroid can usually be well tolerated at the beginning of treatment. Irritability, sleeplessness and headache appear as evidences of thyroid overdosage more frequently in children and adolescents than they do in adults.

*Hypothyroidism in the adult* is diagnosed easily enough as a rule if the possible presence of this condition is constantly kept in mind. A low basal metabolic rate of course in itself does not indicate the presence of hypothyroidism, and improvement in symptoms after the administration of thyroid does not prove the existence of the disorder. These distinctions, however, are somewhat academic and as a rule, thyroid medication is indicated when the metabolic rate is low. When the rate is low and the typical symptoms are present, a positive diagnosis can be made. Ordinarily, physical signs are wanting, and in cases of doubt, the laboratory test which is of greatest value aside from the determination of the basal metabolic rate, is the determination of the blood cholesterol which, when increased to over 250 mg. per hundred cubic centimeters is an important diagnostic aid. The common symptoms—lack of energy and endurance, dryness of the skin and hair and brittleness of the nails, mild edema, paresthesia of hands and feet, a tendency to coldness and relatively diminished memory, and often nervousness—are to be elicited by careful history. Treatment consists of the oral use of desiccated thyroid, one-half to three grains per day as a rule or from five to fifteen grains of whole gland. The clinical signs and symptoms usually are a better guide to therapy than the metabolic rate.

## THE MANAGEMENT OF FUNCTIONAL MENSTRUAL DISORDERS

### DYSMENORRHEA

The etiology of dysmenorrhea is badly understood, and the various theories will not be discussed here. Menstrual pain may be aggravated by constipation, uterine displacements and other factors which increase pelvic congestion. Dilatation and curettage performed empirically where no cause is evident, probably do not give relief in more than 10 or 15 per cent of cases. Constipation should be overcome, and displacements should be corrected. If correction of a displacement by use of a pessary fails to relieve the pain, operation probably will fail also. Exercise is very important. Systematic postural and knee chest exercises or active regular outdoor exercise in young women in whom there is no obvious cause for pelvic pain will sometimes accomplish wonders.

There is a small but definite group of patients in which the dysmenorrhea seems to be due to hypo-ovarianism. The uterus is small and there may be functional sterility. Secondary sex characteristics may give additional suggestive evidence, and assays show low urinary estrin. In these cases, active estrin therapy alone or with prolan will usually give marked relief. Remarkable results are claimed for emmenin. X-ray therapy given in doses of from 10 to 15 per cent of an erythema dose on each of two or three occasions may help. The physiological cure of this type of menstrual pain of course is pregnancy.

If menstrual pain is very severe and especially if it begins before the menstrual flow and leaves abdominal soreness afterward, endometriosis is to be suspected. Even if the disease is localized within the ovary as in the case of a chocolate cyst, very severe pain may be present. Here removal of the affected part will bring relief. At times, fever and elevation of the white cell count may accompany pain from this condition. If the endometrial transplants are diffuse, there is no cure except to render them inactive by removing estrin from the body, either by radiation or by surgical castration.

An unusual type of menstrual pain (Mittelschmerz), which sometimes is associated regularly with bleeding, occurs directly between the normal menstrual periods. This phenomenon which probably is associated with ovulation, may be helped or cured by the use of prolan, and it may be necessary to repeat this regularly at the time the pain is due.

For the treatment of the attack of dysmenorrhea, there is nothing new to offer. Narcotics should not be used. Alcohol which frequently will give great relief must be prescribed with caution. Atropine in moderate doses given regularly for 24 hours preceding and during the attack is sometimes of considerable value. Apart from this, one may advise avoidance of sexual excitement just prior to the menses,

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thorough evacuation of the bowel by cathartic or enema, hot sitz bath, rest, heat locally, and analgesics, such as amidopyrine or acetysalicylic acid or cibalgene (Ciba).

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## THE CONTROL OF PAIN AND COMPLICATIONS FOLLOWING DENTAL OPERATIONS

C. A. RESCH, D.D.S.

For too long a time, the profession and the laity have regarded the removal of a tooth as an inconsequential, simple act which scarcely merited the term "operation." Yet nowhere in the body must an operation be performed under less ideal conditions—the field cannot be kept aseptic, the lack of accessibility and visibility are factors which tend to increase the hazards of traumatization, the skeletal tissue as well as the soft tissues must be disturbed, the pain is amplified by the generous nerve supply from the central nervous system, and finally, the course is laid open for invading organisms to gain the vital centers by approximation to important venous and arterial pathways. In spite of these hazards, the dental profession still is slow to accept the mandates which have been recognized by the other branches of surgery.

From a standpoint of interest, if one follows the history of methods and technique of major operations from an early date to modern times, one sees signs of progress accompanied by statistics which show the ever-increasing curve of success. If one studies the change in the concepts of oral surgery, one notes little actual progress in this phase of dentistry. Progress in the science of dentistry has been steady, but in the majority of cases in which oral surgery is performed, the barber chair in the dentist's office with the mechanical background still serves as the place for the disruption of the physical equilibrium. Therefore, is it any wonder that patients dread the actual removal of a tooth more than a major operation? Yet the consequence of the procedure itself is regarded as insignificant and one of little concern.

If postoperative pain which is due to trauma during a dental operation were expressed by mathematical formula, it would be "in proportion to the general physical resistance and mental reserve of the patient," i. e., the better a patient's health and nervous balance, the less significant is the pain following the trauma which cannot be eliminated entirely in any operation. By the same token, pain and complications which develop following infection are in proportion to the irritation of the causative organisms, which in turn are dependent upon the local resistance of the tissues involved, and again, upon the general resistance of the body. General resistance, to be defined in turn, is an "abstract term to estimate the quality and potentialities of the circulating tissue in maintaining human economy at its optimum."<sup>1</sup>

Infection may follow a dental operation because the surgeon did not observe the physical signs of lowered resistance. It should be an axiom that no oral surgery should be attempted where the cardinal signs of inflammation are present or when the temperature is abnormal, and

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in this regard, how many dental offices are equipped with a thermometer? This instrument usually is conspicuous by its absence in the average office. Therefore, in the presence of lowered resistance or elevated temperature, no surgical procedure should be undertaken, but the condition of the soft tissues should be treated, and the pain controlled by the use of sedatives or opiates.

In all dental operations, we attempt to divide the procedure into three definite parts, the preoperative, operative and postoperative.

*Preoperative treatment* has been given very little consideration by the dental profession, with the result that many patients regard preoperative precautions as unnecessary. Indeed, since it usually is only the force of necessity which drives these patients to the dentist, and this only as a last resort when the physical and mental resistance have been weakened excessively by fatigue, lack of appetite and intermittent pain, preoperative measures should be given the utmost consideration. We feel that a physical examination should be made in each case and that this should include examination of the blood and the urine. Such a routine will assist greatly in the anticipation of the reactions to be expected. We have learned from experience that when the patient seems to have a lowered general resistance, the removal of teeth usually is of secondary importance, and if the internist feels that the patient can withstand the ordeal, he then is hospitalized overnight, and the operation is scheduled for the next day. However, if the physical condition is impaired due to long-standing debilitation, a regimen is prescribed to assist in building up the physical endurance, and the operation is deferred until the general condition is improved. It has been our observation that, regardless of the extent of trauma which is required to remove the oral focal infection, patients who have been hospitalized invariably have less postoperative pain, swelling and bleeding and quicker healing than do those who have the offending tooth removed without any preliminary examination to guide the operator. We ascribed this to the preoperative care which hospitalized patients receive. However, in the group of cases where the physical condition appears to be excellent, and where we are unable to convince the patient of the wisdom of preliminary examination, we proceed to minimize this preoperative phase and hope that postoperative troubles will be small. As this group of patients becomes smaller, greater progress in oral surgery will be assured.

Before extraction is performed, we have found that it is vitally necessary to control the psychological fear and maintain the mental balance of the patient. This is accomplished by telling him exactly what to expect and attempting to portray our ability to overcome obstacles as they may arise. Medication is required in some neurotic types of individuals, and in such cases, we use Nembutal, which ren-

## THE CONTROL OF PAIN FOLLOWING DENTAL OPERATIONS

ders the patient more responsive to the anesthesia and reduces the nervous tension. This also results in less radiated neurosis to the operator.

*Operative procedure:* In the second phase or during the operative procedure, we attempt to reduce trauma to the minimum, although there must be some trauma because no organ of the body can be disturbed without the production of some degree of pain. It is needless to say that sterility of instruments is axiomatic. During the operation, we attempt to keep all saliva and contamination out of the wound by the use of gauze tampons on the floor of the mouth and around the operative field.

If tissues must be cut and bone removed, sharp instruments are necessary, and it should be remembered that tissues should not be cut too near a muscle attachment or in such a manner that the blood supply is disturbed.

In all extractions of teeth, the alveolar processes of the maxillary bones are sprung during the operation. This is a traumatic process which can be minimized, however, if after extraction, the alveolar processes are compressed in place by the fingers which compensates for the spring and assists in reformation and healing.

After extraction, all small spicules or tissue tags should be removed. To accomplish this, the wound may be irrigated gently with a saline solution, and then the flap is tacked into place by sutures to assist in the formation of a blood clot. The formation of this healthy blood clot is very important in minimizing postoperative pain because it effectively seals the socket from food and bacterial debris. The gentle saline irrigation acts in two ways—it removes debris from the area and starts a fresh flow of blood which forms a healthy, sterile clot.

*Postoperative procedure:* We believe that postoperative measures combined with preoperative precautions comprise the most important procedures for the control of pain and complications following extraction of teeth. If the patient has had ample preoperative care, if his physical resistance is known, and if the postoperative phase is followed as outlined, the patient will experience little pain or annoyance in spite of excessive trauma.

Dr. José Aurelio Ortiz<sup>1</sup> of Northwestern University places maximum emphasis on the preoperative stages. In his cases, he used one of the following three methods of immediate postoperative treatment following a simple extraction by forceps with a minimum amount of trauma: (1) The sockets were thoroughly irrigated following extraction and packed with medicated waxes or dressing for the first 24 hours; (2) after the use of an aseptic technique and isolation of the field by gauze tampons, the patient was advised to bite on fresh gauze

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for 10 minutes to insure the formation of a sterile and firm clot before saliva came in contact with the open wound; (3) all these precautions were disregarded; the tooth was extracted with a minimum amount of trauma, and nature was allowed to follow its course. These methods were used following the most simple operative procedure in the extraction of 220 teeth. In 202 instances, healing occurred within the normal span of time regardless of treatment of sockets, and 18 healed in sub-normal time. Apparently the healing time did not depend upon the condition of the tooth. Considering the 18 instances in which there was a delayed healing period, Ortiz reasoned that such a condition was due either to the quality of the blood stream, the resistance of the individual, or the condition of the alveolar bone, which would be altered by the presence of a condensing osteitis or sclerosis of the lamina dura. He concluded, "consequently, if the resistance is high, the disturbing agents are overcome rapidly; if the resistance is low, the other factors merely prolong the course of the struggle. . . . In all instances, it is the quality of the blood that plays the major rôle."

Following extraction, it has been our policy to advise that an ice cap be kept to the face for about two hours. This prevents swelling, pain, and bleeding, and assists in the clot formation. Nothing should be taken into the mouth for a period of three hours, and the patient should refrain from smoking. This allows undisturbed formation of the clot and prevents dislodgment before it has been firmly established. A saline cathartic should be taken, and a liquid diet should be followed for the first 24 hours to assist in the elimination of toxins released by the extraction and to aid in the prevention of undue swelling. In cases of excessive trauma, it is well to use a small dressing of iodoform gauze with Acrithesin, a preparation of Abbott containing anesthesin, trichlorbutinal, acriflavin and eugenol, which has obtundent, antiseptic and tissue-stimulating qualities. For a mouth wash, one-half teaspoonful of salt to 8 ounces of warm water is prescribed, and this is used as frequently as possible after the three-hour period. We do not believe that a socket ever should be packed because this will prevent the formation of the clot, it lengthens the time required for healing, and it is attended by pain and discomfort. All extractions are followed within 24 hours by a radiograph.

If excessive postoperative pain occurs, the cause—local or general—should be determined. If this is found to be a foreign body, it should be removed; if it is due to a so-called "dry socket" in which the clot has been lost and the socket lies open to contaminating agencies, it should be treated locally by gentle irrigations with warm Dakin's solution, warm saline solution or both, followed by a dressing of Acrithesin. We make up a prescription in which Acrithesin is the base, which is mixed with iodoform powder, mercurochrome, and

## THE CONTROL OF PAIN FOLLOWING DENTAL OPERATIONS

powdered Dakin's tablet. This is used on sterile gauze which is placed in the wound, and is usually sufficient to give almost immediate relief. The socket should be irrigated daily and the dressing changed. If there is an increase of swelling with a rise in temperature in addition to pain, the patient should be hospitalized, hot saline mouth wash prescribed, packs of saturated solution of magnesium sulphate should be applied to the affected side, and an incision for drainage should be made when the temperature falls.

### COMPLICATIONS

One of the complications which follows extraction which has a serious aspect and grave prognosis is osteomyelitis, an infection of the medullary portion of the bone. It is characterized by the symptoms of fever, swelling with trismus and general malaise. In the early stages of the disease, radiograms show no abnormality and are of little value in making a diagnosis, but in the suppurative stages they do show the extent of the infection. In treating this complication, we use hot saline irrigation intraorally and hot salinated solution of magnesium sulphate extraorally, which assists in organization. When the fever drops, and the area is fluctuant, the wound is opened and drained.

Osteomyelitis may lead to another complication, which although it is rare, may follow dental operations—namely, cavernous sinus thrombosis. This is characterized by a high fever curve, rapid pulse, general prostration, prominence of the veins near the eye associated with increasing proptosis of eyeball, slight headache and rigid neck. Usually within 48 hours after the onset of the latter symptoms, the conjunctiva begin to protrude in yellowish folds, vomiting occurs, and the patient lapses into coma and dies. The mortality from this disease is very high. Stewart<sup>2</sup> states, "Death is practically certain without an operation, while the mortality after operation is about 50 per cent." The etiological factor is the *Staphylococcus*, and symptoms of meningitis and septicemia are present. At autopsy, metastatic abscesses may be found in various parts of the body, particularly the lungs.

A third complication is Gensoul's disease or Ludwig's angina which occurs in the soft tissues of the floor of the mouth in the form of cellulitis which may be an extension of an infection of the submaxillary gland. It is very difficult to determine early whether an existing cellulitis will develop to the extent of being classified in this serious category. The condition progresses rapidly, however, and within three or four days, the neck becomes so swollen and painful that respiration is difficult. The tongue is found to be thick and swollen and trismus is very marked. This is accompanied by high temperature and symptoms of infection. Disturbances of the circulation may be so great that a localized gangrene may result and dyspnea may be caused by pres-

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sure on the trachea. In the early stages it is difficult to distinguish this from a cellulocutaneous or phlegmonous erysipelas. The prognosis is not favorable, and it has been estimated that about 40 per cent of the cases terminate fatally. Mead<sup>3</sup> states that "there is good reason to believe the Ludwig's angina and noma are the terminal local results of infection starting as a cellulitis or adenitis in patients of lowered resistance. In other words, cellulitis and adenitis in patients of good resistance when proper treatment is applied, usually respond to treatment. In other cases, in which the general resistance is low, in spite of proper treatment, the condition may extend to a more severe type of local destruction or gangrene with the classical picture of either a Ludwig's angina or noma."

These complications may occur without the trauma attending dental operations, because they are dependent to a large measure upon the general physical condition, and when they do occur following dental operations, regardless of whether the trauma is the etiological factor, the surgeon assumes the liability. Thus, it behooves the oral surgeon to use all the preoperative precautions possible to prevent such occurrences, and by making this a routine procedure, he should have sufficient control over the postoperative course to cause the patient little pain or discomfort.

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## PERFORATION OF AN ACUTE PEPTIC ULCER

### Report of a Case\*

T. E. JONES, M.D., AND J. H. YANT, M.D.

The following case is reported because perforation of an acute peptic ulcer had occurred 24 hours before operation was performed.

The patient was a man who was admitted to the Cleveland Clinic Hospital about 6:00 p. m. on August 15, 1934. His chief complaint was of "pain in the abdomen." At 8:00 p. m. on the preceding day, excruciating pain in the epigastrium suddenly occurred while the patient was lying down. This was so severe that it made the patient jump up, and then he was doubled over from pain. Vomiting and a cold, clammy sweat followed, and the pain soon became somewhat less intense. During the night the patient felt better, although he had generalized abdominal discomfort. In the morning, the pain became more severe and seemed to be localized somewhat in the right upper abdominal quadrant. The family physician made a diagnosis of acute cholelithiasis, and morphine was administered hypodermically. This eased the pain slightly, but as the day progressed, the pain increased in severity, and another hypodermic did not relieve it to any appreciable extent.

The past history was irrelevant except that vague gastro-intestinal symptoms had been present for several years, and diagnoses which varied from colitis to disease of the gall bladder had been made.

Physical examination at the time of admittance revealed an asthenic type of individual, 50 years of age, who had anxious facies. The pupils were almost pin-point in size and showed little, if any, reaction—this undoubtedly was due to the morphine which had been administered. The tongue was only moderately moist. An adenoma of the right lobe of the thyroid was present, and the excursions of the thorax were limited by the abdominal pain.

Examination of the abdomen revealed it to be board-like—the rigidity was slightly more marked in the upper quadrants. While tenderness was present throughout, this was more pronounced in the right upper quadrant just beneath the costal margin. Liver dullness was obliterated. The temperature was 98.6° F., and the pulse rate was 130 per minute. No other abnormalities were found. A diagnosis of perforated peptic ulcer was made, and the patient was prepared for operation.

A vein in the region of the left ankle was exposed, and the continuous intravenous administration of glucose was inaugurated. When the peritoneum was opened through an upper right rectus incision, gas escaped and quantities of greenish gray, cloudy fluid, and what

\*Reported at a Wednesday Evening Staff Meeting.

appeared to be gastric contents, welled up into the incision. This was aspirated, and depression of the liver border revealed a large collection of fluid—possibly 12 ounces—between the liver and the diaphragm. This fluid was aspirated also. There were numerous, easily broken adhesions in the region between the pylorus, the omentum, and the gall bladder, and when these adhesions were freed, more of the same type of fluid appeared. Upon exposure of the pylorus and duodenum a perforation about one-half inch in diameter was found on the anterior surface just at the pyloric ring. A plication was performed, and a piece of omentum was sewed over this area. A thorough toilet of the upper abdomen was made with normal saline solution. Two cigarette drains, one near the site of the ulcer, and the other in the left sub-diaphragmatic area, were put in place, and the abdomen was closed. A McBurney's incision was made on the right side, and upon opening the peritoneum, a large quantity of fluid similar to that encountered previously was evident. This was aspirated as thoroughly as possible, and two cigarette drains were placed into the pelvis. Through a left McBurney's incision, the same welling up of fluid was encountered, and this was treated in a similar manner, one drain being placed into the pelvis and another lateral to the mesosigmoid.

Postoperatively, to combat the peritonitis and the possible occurrence of paralytic ileus, hot stupes were applied to the abdomen, and one cubic centimeter of pitressin was administered every four hours for three days. On the first morning after operation, transfusion of 500 cc. of whole blood was given. From 3,000 to 3,500 cc. of 10 per cent glucose solution was alternated with physiological saline solution by the continuous intravenous route daily. This was discontinued on the fifth postoperative day, and the surgical Sippy routine was begun. On the fifth postoperative day, a wound infection developed which was drained. The drains into the peritoneal cavity and in the McBurney's incisions were shortened and finally removed on the tenth and on the twelfth postoperative days respectively. The patient's maximum temperature was 101.2° F., and it became normal on the ninth day postoperatively and remained there throughout the remainder of the hospitalization.

At the time of discharge, the patient was instructed to remain at rest in bed for at least another week, and a surgical Sippy diet was prescribed. A recent report from this patient informs us that he is making a satisfactory convalescence.

The immediate diagnosis of perforation of a peptic ulcer is very important because with each hour of delay, the chance for recovery becomes less and the death rate rises rapidly after perforation has been present twelve hours. In a series of seventy-five cases reported by James and Matheson,<sup>1</sup> the mortality was 100 per cent in those cases

## PERFORATION OF AN ACUTE PEPTIC ULCER

where perforation had been present for more than 24 hours before operation. Probably the two most important conditions to be differentiated from a perforated ulcer of this duration are cholelithiasis with biliary colic and an acutely inflamed appendix which has ruptured. The initial pain which is associated with perforation of an ulcer occurs one or two hours after eating when the stomach is full, or at the time of some vigorous exercise. The tenderness and rigidity is more marked and widespread than in biliary colic. The location of the point of maximum tenderness, the sudden onset of excruciating pain, and obliteration of liver dulness should indicate perforation of a peptic ulcer. In this case, the point of maximum tenderness was beneath the costal margin and not in the appendiceal region.

That the absence of liver dulness is not pathognomonic of perforated ulcer is illustrated by a case which recently was observed here in which a diagnosis of peptic ulcer had been made several years previously. At our recent examination, in addition to the findings which indicated the presence of an acute perforation, obliteration of liver dulness was noted and a diagnosis of acute perforation of peptic ulcer was made. Immediate operation revealed a ruptured gangrenous appendix.

The treatment of peptic ulcer from eighteen to twenty-four hours after perforation is, of course, immediate operation. In recent years, the treatment of choice has been a simple plication of the ulcer with reinforcement by omentum of the suture line. As much of the fluid and gastric contents as possible should be aspirated from the peritoneal cavity, because the fluid is no longer sterile. This includes a careful toilet with normal saline solution at the site of the ulcer, and beneath the diaphragm because sub-diaphragmatic abscess is a fairly common complication of this condition. In spite of the trend to close the peritoneum without drainage, we believe it is advisable to use drainage, because in such a case as this, if the McBurney's incisions had not been made and the soft rubber drains inserted, the intestines would have been bathed in purulent material, which undoubtedly would lead to peritonitis and obstruction.

When perforation has been present for as long as 24 hours, the patient is a poor surgical risk. The general condition should be supported during operation by the continuous intravenous administration of 10 per cent glucose and normal saline solutions. This is started before operation and continued for several days. Blood transfusions also should be used when indicated. Postoperatively, the occurrence of paralytic ileus must be combated, and this was done efficaciously in this case by the use of hot stupes and pitressin.

Dependent upon the condition of the abdomen, food by mouth

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should gradually be taken on some plan such as the surgical Sippy routine. After discharge from the hospital, adequate follow-up treatment should begin, and the routine for the management of ulcers should be prescribed, because recurrence of the ulcer may occur. We feel that thorough removal of as much fluid as possible over the liver and in the pelvis contributed greatly to the favorable result in this case.

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- William E. Lower: Disturbances of the gastro-intestinal tract associated with diseases of the genito-urinary tract.  
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- William V. Mullin: Surgical indications in diseases of the nasal sinuses due to allergy.
- William V. Mullin and Leigh L. Darsie: Carcinoma of the larynx: A study of 133 cases.
- Robert S. Dinsmore and George Crile, Jr.: Thyroid problems and end-results of operations on the thyroid gland.
- Robert S. Dinsmore: Tuberculosis of the thyroid gland.
- James A. Dickson: The treatment of tuberculosis of the hip in children.
- W. James Gardner: The diagnosis of surgical lesions of the brain: Analysis of 100 consecutive cases.
- E. N. Collins: Is the gastric ulcer benign or malignant?
- Charles C. Higgins: The medical management of urinary lithiasis.
- Wallace Duncan and D. W. Coughlan: Disease of the sacro-iliac joint. A study of 400 cases.
- U. V. Portmann: The indications for irradiation in the treatment of malignant tumors.
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- Alexander T. Bunts: Spinal cord tumors. An analytical review of thirty-six cases.
- W. J. Engel: Types of prostatic hypertrophy with relation to surgical treatment.

## **THE FRANK E. BUNTS EDUCATIONAL INSTITUTE**

As announced in the July number of the Quarterly, The Frank E. Bunts Educational Institute will offer a postgraduate review course on "The Diagnosis and Treatment of Diseases of the Glands of Internal Secretion" on November 11, 12 and 13, 1935, at the Cleveland Clinic.

A complete outline of the course and application blank will be found on succeeding pages of this Quarterly.

### **Facilities**

The Cleveland Clinic, the Research Department, and the Cleveland Clinic Hospital will be available for use. The Cleveland Clinic Library is well equipped with all standard reference books and with current periodicals.

### **Hotels**

Several hotels near the Clinic are reasonable in price and excellently managed. The Hotel Bolton, Wade Park Manor, Park Lane Villa and Fenway Hall are close to the Clinic. Downtown hotels are the Cleveland, the Statler, the Hollenden and the Carter.

### **Parking**

Sufficient parking space is available on the grounds of the Clinic and a number of garages are in the neighborhood.



## DIAGNOSIS AND TREATMENT OF DISEASES OF THE GLANDULAR SYSTEM

Thyroid, Parathyroid, Pituitary, Pancreas, Ovaries, Adrenals and  
Therapy with Testicular Hormone

**Monday, November 11th, 1935**

### THE THYROID GLAND

8:00- 9:00 A. M.	Registration _____	
9:00-10:00 A. M.	Surgical Anatomy of the Thyroid Gland _____	R. S. DINSMORE, M. D.
10:00-11:00 A. M.	Applied Physiology of the Thyroid Gland _____	D. R. McCULLACH, Ph. D.
11:00-12:00 Noon	Gross and Microscopical Pathology of the Thyroid Gland _____	A. GRAHAM, M. D.
12:00 Noon- 1:00 P. M.	Luncheon _____	
1:00- 1:30 P. M.	Demonstrations and Exhibits _____	
1:30- 3:00 P. M.	Differential Diagnosis and Treatment of Diseases of the Thyroid Gland _____	E. P. McCULLACH, M. D.
3:00- 3:30 P. M.	The Heart in Thyroid Disease _____	A. C. ERNSTENE, M. D.
3:30- 3:45 P. M.	Eye Changes in Thyroid Disease _____	A. D. RUEDEMANN, M. D.
3:45- 4:00 P. M.	Laryngeal Changes in Thyroid Disease _____	W. L. DEETON, M. D.
4:00- 5:00 P. M.	Psychoses Associated with Thyroid Disease _____	L. J. KARNOSH, M. D.
8:00 P. M.	Frank E. Bunts Lecture _____	DAVID MARINE, M. D., Montefiore Hospital, New York City.

**Tuesday, November 12th, 1935**

### THE THYROID GLAND

9:00 A. M.-12:00 Noon	Operative Clinics: Surgery of the Thyroid Gland _____	G. CRILE, M. D. R. S. DINSMORE, M. D.
9:00 A. M.-12:00 Noon	Refinements in the Surgical Technic of Thyroidectomy _____	R. S. DINSMORE, M. D.
	Pre- and Post-operative Care of the Patient with Thyroid Disease _____	J. H. YANT, M. D.
	Presentation of Cases _____	G. CRILE, JR., M. D.
	Mortality from Thyroid Disease _____	G. CRILE, JR., M. D.
	Diseases of the Thyroid Gland in Children _____	R. S. DINSMORE, M. D.
	Roentgen Diagnosis of Diseases of the Thyroid Gland _____	B. H. NICHOLS, M. D.
12:00 Noon- 1:00 P. M.	Luncheon _____	
1:00- 1:30 P. M.	Demonstrations and Exhibits _____	

## Tuesday, November 12th, 1935—Continued

### THE PANCREAS AND OVARIES

1:30- 3:00 P. M.	Disease of the Pancreas with Special Reference to Diabetes _____	E. P. McCULLAGH, M. D.
3:00- 3:30 P. M.	Orthopaedic Surgery of the Diabetic _____	J. A. DICKSON, M. D.
3:30- 4:30 P. M.	Dysfunction of the Ovaries with Special Reference to Disturbances of Menstruation _____	E. P. McCULLAGH, M. D.
4:30- 5:00 P. M.	Surgery of the Ovary _____	T. E. JONES, M. D.
8:00 P. M.	Frank E. Bunts Lecture "Diagnosis and Therapeutic Problems of the Menopause" _____ Discussion.	E. L. SEVERINGHAUS, M. D., Associate Professor of Medicine, University of Wisconsin.

## Wednesday, November 13th, 1935

### THE PITUITARY, PARATHYROID AND ADRENAL GLANDS

9:00-10:30 A. M.	Diagnosis and Treatment of Diseases of the Pituitary Gland _____	E. P. McCULLAGH, M. D.
10:30-10:45 A. M.	Ocular Findings in Pituitary Disease _____	A. D. RUEDEMANN, M. D.
10:45-11:00 A. M.	Roentgen Examination of the Sella Turcica in Pituitary Disease _____	B. H. NICHOLS, M. D.
11:00-12:00 Noon	Surgical Diagnosis and Treatment of Pituitary Disease _____	W. J. GARDNER, M. D.
12:00 Noon-1:00 P. M.	Luncheon _____	
1:00- 1:30 P. M.	Demonstrations and Exhibits _____	
1:30- 2:00 P. M.	Presentation of Cases _____	A. T. BUNTS, M. D.
2:00- 2:30 P. M.	X-ray Therapy of the Pituitary Gland _____	U. V. PORTMANN, M. D.
2:30- 3:00 P. M.	Diseases of the Parathyroid Glands _____	E. P. McCULLAGH, M. D.
3:00- 3:30 P. M.	Anatomy and Physiology of the Adrenal Glands _____	D. P. QUIRING, M. D.
3:30- 4:00 P. M.	Diseases of the Adrenal Glands _____	E. P. McCULLAGH, M. D.
4:00 P. M.	Adrenal and Sympathetic Complex _____	G. CRILE, M. D.

*The Following Demonstrations of Laboratory Technic  
will be given Each Day from 1 to 1:30 P. M.*

Friedman Tests _____	W. Kenneth Cuyler, M. A.
Blood Iodine _____	D. R. McCullagh, Ph. D.
The Use of the Oxygen Tent _____	J. H. Yant, M. D.

*The Following Exhibits will be open each day*

X-ray Studies of the Sella Turcica _____	B. H. Nichols, M. D.
X-ray Studies of Substernal Goiter _____	B. H. Nichols, M. D.
Pathological Specimens of Diseased Thyroid Glands _____	A. Graham, M. D., and G. Crile, Jr., M. D.
Colored Lantern Slides of Blood Cells _____	R. L. Haden, M. D.

